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Title: Open Label Pilot Study of 2% Tofacitinib for the Treatment of Refractory Vitiligo

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Introduction

Treatment options for vitiligo are limited and many cases remain refractory to first and second line treatments. Interferon-gamma signaling mediated by Janus kinase (JAK) has been implicated in the pathogenesis of vitiligo.¹ Systemic administration of tofacitinib, a potent JAK1/3 inhibitor, has been effective in treating vitiligo in case reports,² however, it is associated with infections, malignancies, cytopenias, gastrointestinal perforations, and hyperlipidemia in some patients with rheumatoid arthritis. Topical administration of tofacitinib may limit unintended systemic effects, and herein we present the experience with topical tofacitinib 2% cream in the treatment of patients with non-segmental vitiligo.

Material and Methods

This nonrandomized cohort study was conducted in collaboration between the Department of Dermatology at Brigham and Women's Hospital, Boston, Massachusetts and the Department of Dermatology at the University of California, Irvine. The Institutional Review Boards at both institutions approved this protocol. Prescription records were reviewed for patients receiving a prescription for 2% topical tofacitinib cream compounded in a liposomal cream by ChemistryRx in Philadelphia. Patients were prescribed tofacitinib 2% cream twice daily to target areas. Concomitant treatment with topical steroids, topical

calcineurin inhibitors, supplements (e.g. *Polypodium Leucotomos* and *Gingko biloba*), or phototherapy was allowed. Patients who received concomitant phototherapy received one of the following: booth NBUVB, PUVA, or excimer laser treatment. Corresponding medical records including clinical notes and photographs were reviewed. The primary outcome measure was the change in pigmentation of treated target lesions as measured by BSA. A two-tailed, two sample t-test was used to evaluate the relationship between categorical variables and repigmentation of target lesions. A simple linear regression was used to evaluate the relationship between age of onset and duration of disease with repigmentation.

Results

Sixteen patients with vitiligo received prescriptions for 2% tofacitinib cream and were evaluated during a follow-up visit. Half the patients were female, and the ethnic distribution was: 10 Caucasians, 1 Latino, 1 East Asian, and 4 South Asians. Seven patients were Fitzpatrick type II, 4 were type III, 2 were type IV, and 3 were type V. Three patients had focal facial vitiligo, 2 had focal non-facial vitiligo, while 11 had generalized vitiligo. The mean age was 55.125 [16-78]. Average follow-up time was 153 days [63-367]. The average length of time since onset of vitiligo was 13.9 years. All but one patient was previously treated with topical steroids, topical calcineurin inhibitors, and/or phototherapy. Thirteen experienced repigmentation with 4 patients experiencing >90% repigmentation; 5 patients experiencing 25-75%

repigmentation; and 4 patients experiencing 5-15(%) repigmentation. Two patients experienced no change; and 1 patient experienced slow progression of depigmentation in the target lesion (Table 1). Facial lesions improved more than non-facial lesions ($p=0.0216$), and patients with Fitzpatrick skin type IV-VI improved more than individuals with lighter skin types ($p=0.03434$). Gender ($p=0.8327$) and age at diagnosis ($r = -0.2232$) were not correlated with repigmentation. There was a moderate negative correlation of duration of disease with repigmentation ($r = -0.4669$).

Acne-like papules on the face were reported by 1 patient. These lesions resolved with cessation of the medication. One patient reported subtle skin contour changes on his chin which led to cessation of treatment after 2 weeks. No other adverse events were reported.

Discussion

Herein we present a series of 16 patients with vitiligo treated with topical tofacitinib. Topical JAK inhibition offers the promise of targeted therapy with minimal systemic side effects, however, the published experience to date is limited to 9 patients treated with ruxolitinib³ and a series of 11 patients treated with tofacitinib for facial vitiligo.⁴ This series extends previous observations and demonstrates the potential of benefit for at least some patients with non-facial lesions.

Consistent with previously published results, robust responses were noted on facial lesions. We also noted greater responses in patients with darker skin types. While effects on non-facial lesions were minimal (average of 16% repigmentation), 5 of 8 patients treating non-facial targets experienced some improvement. One patient experienced 95% repigmentation of focal lesions in the axilla and on the right torso. This patient was 16-years-old at the age of treatment, was Fitzpatrick Skin Type V, and had only focal lesions occupying <1% BSA, suggesting that topical tofacitinib may be effective for non-facial lesions if the patient exhibits other favorable prognostic indicators (e.g. younger age, darker skin type, and focal disease). In contrast with previously reported studies suggesting that concomitant light exposure may be required for response,⁵ there was not a clear pattern in our series with respect to response and concomitant phototherapy. Our study may not have been sufficiently powered to detect the effect of phototherapy, however.

While this study is small, uncontrolled, and occurred in the setting of concomitant treatments, it suggests that topical administration of tofacitinib is safe and efficacious. Future randomized controlled studies or larger cohorts should be performed to confirm these observations and identify patients most likely to benefit from JAK inhibition.

Acknowledgments

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Table 1. Clinical characteristics, concurrent treatments, and response

	Age	Ethnicity	Skin Type	Length of Diagnosis (years)	Facial Lesions (treated)	Non-facial Lesions	Concurrent treatments						Response (% repigmentation of target lesion)
							NBUV B / Excimer	PUVA	Systemic Steroid	Topical Steroid	Topical Calcineurin Inhibitor	Herbals	
1	68	Caucasian	II	10	✓	✓	✓						34
2	68	Caucasian	III	31		✓		✓					10
3	64	Caucasian	III	12		✓	✓						6
4	65	Caucasian	III	13	✓		✓						66
5	71	Caucasian	II	2	✓		✓						39
6	70	South Asian	IV	0.5	✓		✓						65
7	63	Caucasian	II	58		✓	✓						-2
8	57	South Asian	V	22		✓							5
9	44	South Asian	V	1	✓						✓		90
10	29	Hispanic	IV	19	✓		✓						95
11	67	Caucasian	II	21	✓							✓	0
11	35	Caucasian	II	1	✓	✓							100

2		an											
1 3	38	Caucasi an	II	8	✓						✓		30
1 4	16	South Asian	V	10		✓				✓	✓		95
1 5	73	East Asian	III	11		✓				✓			15
1 6	54	Caucasi an	II	3		✓				✓	✓		0

