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Repigmentation in vitiligo using the janus kinase inhibitor, tofacitinib, may require concomitant light exposure

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Abstract

BACKGROUND—Vitiligo is an autoimmune disease wherein cutaneous depigmentation occurs. Existing therapies are often inadequate. Prior reports have shown benefit of the Janus kinase (JAK) inhibitors.

OBJECTIVE—To evaluate the efficacy of the JAK 1/3 inhibitor, tofacitinib, in the treatment of vitiligo.

METHODS—This is a retrospective case series of 10 consecutive patients with vitiligo treated with tofacitinib. Severity of disease was assessed by body surface area of depigmentation.

RESULTS—Ten consecutive patients were treated with tofacitinib. Five patients achieved some repigmentation at sites of either sunlight exposure or low-dose nbUVB. Suction blister sampling revealed that the autoimmune response was inhibited during treatment in both responding and non-responding lesions, suggesting that light was primarily required for melanocyte regeneration, rather than immunosuppression.

LIMITATIONS—Limitations include the small size, retrospective nature, and lack of a control group.

CONCLUSION—Treatment of vitiligo with JAK inhibitors appears to require light exposure. In contrast to treatment with phototherapy alone, repigmentation during treatment with JAK inhibitors may require only low-level light. Maintenance of repigmentation may be achieved with

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JAK inhibitor monotherapy. These results support a model wherein JAK inhibitors suppress T cell mediators of vitiligo and light exposure is necessary for stimulation of melanocyte regeneration.

Keywords

Janus kinase; JAK; tofacitinib; ruxolitinib; vitiligo; narrowband ultraviolet B; nbUVB; phototherapy

INTRODUCTION

Vitiligo is a chronic autoimmune disease that results from the destruction of melanocytes, causing white spots on the skin. Vitiligo affects approximately 1% of people worldwide and can affect both adults and children, causing diminished quality of life and marked psychological distress.^{1–4} Treatments include topical corticosteroids and calcineurin inhibitors, but the most effective treatment and mainstay of therapy is narrowband ultraviolet B (nbUVB) phototherapy.^{5–10} However, incomplete response to treatment is common.

The pathogenesis of vitiligo involves the destruction of melanocytes via cell-mediated immunity, and studies show that IFN- γ and CD8⁺ T cells play a key role in this process.^{7,11–16} A similar pattern of CD8⁺ T cell-driven autoimmunity is also seen in alopecia areata,¹⁷ a disease that often co-occurs with vitiligo, suggesting that targeted therapy in one disease may be effective in the other.¹⁸ Recently, 2 case reports described successful repigmentation in vitiligo, one using tofacitinib, a Janus kinase (JAK) 1/3 inhibitor,¹⁹ and another using ruxolitinib, a JAK 1/2 inhibitor,²⁰ presumably via inhibition of IFN- γ signaling in the skin. A case series reported efficacy of topical ruxolitinib in vitiligo patients, in particular for facial involvement.²¹

Here we report the results of 10 consecutive patients with vitiligo treated with oral tofacitinib.

METHODS

This study is a retrospective case series of 10 patients seen between July 2014 and January 2017. Medical records of patients with vitiligo, aged 18 years and older, treated with tofacitinib for at least 3 months were reviewed. Clinical and demographic information, including biological sex, age, disease duration and course, medical history, family history, and prior treatments were collected. Before initiating tofacitinib, all patients underwent baseline laboratory evaluation including comprehensive metabolic panel, complete blood cell count with differential, fasting lipid panel, QuantiFERON-TB Gold (Cellestis Limited, Melbourne, Australia), and screening for HIV and hepatitis B and C. Body surface area (BSA) of depigmentation was assessed prior to and at the end of treatment. Serial laboratory monitoring, physical exams, and review of systems were used to monitor for adverse events.

Suction blister sampling was performed in one patient before beginning tofacitinib and then again 10 months later to assess changes in T cell recruitment and chemokine expression. Three sites were selected for sampling – one was a site of vitiligo that did not previously

respond to treatment with tofacitinib, one was a recently active site (featuring confetti depigmentation²²) that previously responded to tofacitinib, and one was unaffected skin.

Suction Blister Sampling and Processing

The Negative Pressure Instrument Model NP-4 (Electronic Diversities, Finksburg, MD) was used to induce suction blisters (1 cm in diameter). Blisters formed at a pressure between 10–15 mm Hg negative pressure and at a constant temperature of 40°C. Once blisters formed, the blister fluid was aspirated through the roof using a 1 mL insulin syringe. Cells in the blister fluid were pelleted at $330 \times g$ for 10 minutes and prepared for flow cytometry. The supernatant of the blister fluid was stored at –80°C until analysis by enzyme-linked immunosorbent-assays (ELISA) for chemokines. None of the blisters were hemorrhagic.

ELISA

Chemokines were assayed using the Human CXCL9/MIG DuoSet ELISA (DY392) and Human CXCL10/IP-10 DuoSet ELISA (DY266, R&D Systems) per the manufacturer's instructions. Optical densities were measured using a Perkin Elmer EnVision 2102 multilabel reader and analyzed using a 4 parameter logarithmic standard curve.

Flow Cytometry

Cells were blocked with Human TruStain and incubated with an antibody cocktail for 30 minutes at 4°C. Anti-human CD45 (2D1) and CD 8 (SK1) were used at 1:20 dilution. Anti-human CD3 (OKT3) was used at 1:200 dilution (BioLegend) and Fixable Viability Dye eFluor 455UV at 1:1000 (Ebioscience). Prior to cell staining in the PBMCs, 10^6 PBMCs were treated with desatinib for 30 minutes at 36°C, pelleted and incubated with Mart-1 Pentamer (ProImmune, 082) for 10 minutes at room temperature.

RESULTS

Patient characteristics

All 10 patients in this case series were adults. Duration of disease was 4–33 years (mean 16.6, SD, standard deviation, 8.8). Eight patients had generalized vitiligo and 2 patients had primarily acral involvement, with 1–100% BSA. Additional patient characteristics, together with previous treatments, are described in Table 1.

Clinical response to treatment

Ten patients underwent treatment with tofacitinib 5–10 mg QD-BID for an average of 9.9 months (SD 4.1, range 3–15). A mean decrease of 5.4% BSA involvement with vitiligo was observed in 5/10 patients, while the other 5 patients did not achieve any repigmentation.

In the 5 patients who achieved some reversal of disease, repigmentation occurred only in sun-exposed areas of skin in 3 of them, diffusely in another patient undergoing concomitant full-body nbUVB phototherapy, and to the dorsal hands in another patient after starting concomitant hand nbUVB phototherapy. Table 2 summarizes the clinical course of each patient.

Of the 5 patients who did not experience repigmentation, only one reported significant sunlight exposure, and the others either avoided sunlight or practiced photoprotection.

Adverse events

The most common adverse event was upper respiratory infection in 2 patients. One patient reported weight gain of 5 pounds and one patient reported arthralgias. Mild elevations of lipids were noted in 4 patients. There were no serious adverse events.

Suction Blister Sampling

Previous analysis of suction blisters of active vitiligo lesions demonstrated that T cell number and CXCL9 protein level were both sensitive and specific to predict disease activity.¹⁵ We used this method to measure the treatment response of patient 1 who had previously responded to tofacitinib but then relapsed after discontinuing treatment.¹⁹ Prior to re-treatment with tofacitinib, she underwent suction blister sampling of a previously treatment-unresponsive site (intermammary chest), a previously treatment-responsive site (forearm), and skin unaffected by vitiligo (arm). After 10 months of tofacitinib, she underwent blister sampling again at the same sites, where responses to re-treatment were the same as with the original treatment, i.e., no repigmentation of the intermammary chest and repigmentation of the forearm were observed.

A small number of T cells was detected in all sites at baseline as well as during treatment. At baseline, there were 29 CD8⁺ T cells in the previously non-responding lesion and a greater number in the recently developed lesion (69 cells). Both lesional sites had more cells than in unaffected skin. Following treatment with tofacitinib, absolute numbers in each site were reduced (Figure 2A and 2B). Similarly, melanocyte-specific T cells (HLA pentamer positive) were detected in the PBMCs at baseline, and this percentage did not change with tofacitinib treatment, and even increased slightly (Supplementary Figure 1A).

CXCL9 was elevated in all 4 lesional blisters (2 blisters were induced and sampled at each site) compared to unaffected skin at baseline (Figure 2C), and CXCL10 was elevated in 3 of 4 lesional blisters (Figure 2D). Following treatment, chemokine levels became undetectable in both the blister fluid (responding and non-responding sites, Figures 2C–D), and serum (Supplementary Figure 1B).

In summary, tofacitinib effectively decreased T cell numbers and chemokine proteins (a measure of IFN- γ signaling) in the skin. In the blood, tofacitinib did not affect the number of autoreactive T cells but did decrease chemokines.

DISCUSSION

The pathogenesis of vitiligo involves CD8⁺ T cell production of IFN- γ , which leads to CXCL9/10 expression by keratinocytes and further recruitment of CD8⁺ T cells, resulting in melanocyte destruction.^{7,13–16,23} Originally, we hypothesized that inhibition of IFN- γ signaling using JAK inhibitors would lead to repigmentation, and results of 2 patients^{19,20} using 2 different oral JAK inhibitors, tofacitinib and ruxolitinib, supported this hypothesis. Recently, a case series evaluating topical ruxolitinib also demonstrated efficacy²¹.

Interestingly, both of the patients taking oral JAK inhibitors repigmented mainly in sun-exposed areas, and the topical study reported the best response on the face, also a sun-exposed location. Here we report the results of 10 patients in whom treatment with tofacitinib only led to repigmentation when there was concomitant light exposure, either sunlight or nbUVB phototherapy. Notably, the low doses of nbUVB that were beneficial would not typically be effective as monotherapy in vitiligo.

There are several important observations that emerge from this series of patients.

- Tofacitinib treatment of vitiligo appears to require light exposure, for which low doses may be sufficient. Even regular exposure to sunlight was sufficient to achieve repigmentation in some patients.
- Repigmentation may again be achieved after depigmentation recurs upon discontinuation of tofacitinib.
- Areas of repigmentation are maintained with tofacitinib monotherapy after light exposure ceases.
- Tofacitinib treatment in one patient eliminated IFN- γ signaling and reduced T cell numbers in the skin, even in lesions that did not repigment.
- Suction blister sampling may be used to understand the effects of treatment on the immunological milieu of the skin.

Altogether, these results lead to the model shown in Figure 3. Repigmentation requires both suppression of inflammation in the skin, which is achieved with JAK inhibitor treatment, and melanocyte stimulation via light exposure. The requirement for only low-dose nbUVB phototherapy or sunlight to induce repigmentation while on tofacitinib suggests that the higher doses of nbUVB required to induce repigmentation in vitiligo patients may specifically be required for the immunosuppressive effect. It may be that high doses are required to suppress autoimmunity in the skin, but that low doses are sufficient to promote melanocyte regeneration; future studies are needed to test this hypothesis. The lack of response of patient 8, who received both tofacitinib and sun exposure, highlights that there are yet unidentified factors influencing treatment response. For instance, IFN- γ signaling is mediated by JAK1/2, and therefore tofacitinib, a JAK1/3 inhibitor, may be less efficacious than a JAK1/2 inhibitor, such as ruxolitinib. Adverse events were mild and infrequent, which is consistent with other studies of off-label use of tofacitinib in skin diseases.^{24–26}

Treatment with JAK inhibitors together with light exposure may be an effective targeted treatment for vitiligo. In this series, JAK inhibitor monotherapy does not appear to be efficacious, but JAK inhibitors in combination with either low-dose nbUVB phototherapy or sun exposure leads to repigmentation. Prospective clinical trials are needed to further assess JAK inhibitor treatment of vitiligo.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

nbUVB	narrowband ultraviolet B
IFN-γ	Interferon- γ
AA	alopecia areata
JAK	Janus kinase
BSA	body surface area
SD	standard deviation
CXCL	C-X-C motif chemokine ligand
PBMCs	peripheral blood mononuclear cells

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Figure 1. Clinical images of patient 1: A) The sun-exposed forearm and dorsal hand, before and during treatment, demonstrates repigmentation. B) The chest, before and during treatment, under room light (top panels) and Wood's lamp (bottom panels), demonstrates repigmentation of sun-exposed lesions involving the upper chest but not sun-protected lesions involving the intermammary chest.

Figure 2.

CD8⁺ T cell quantification and chemokine protein levels in blister fluid in patient 1. A) Representative CD8⁺ T cells in the CD8⁺ gate for each site at baseline and after treatment. CD8⁺ T cells were first gated on singlets and then by physical parameters SSC and FSC, all live cells, all CD45⁺ cells, all CD3⁺ cells and all CD8⁺ T cells. B–D) Comparison of CD8⁺ T cell number (B), CXCL9 (C) and CXCL10 (D) in each site before and after treatment. R = responding site, NR = Non-responding site, NL = non-lesional site.

Figure 3.

Model of vitiligo treatment with JAK inhibitor plus light exposure.

Interferon (IFN)- γ (blue circles) signals through the IFN- γ Receptor (IFN- γ R) via Janus kinase (JAK) 1 and JAK2, initiating phosphorylation of Signal Transducer and Activator of Transcription 1 (STAT1) and translocation to the nucleus where IFN- γ dependent genes, including C-X-C motif chemokine ligand (CXCL) 9 and CXCL10 are transcribed. CXCL9 and CXCL10 recruit autoreactive CD8⁺ T cells to the skin where they attack melanocytes, leading to depigmentation (white keratinocytes). Tofacitinib inhibits this process by blocking JAK signaling. Even under JAK inhibitor suppression of vitiligo, repigmentation depends on photoactivation to stimulate melanocytes to leave their stem cell niche in the hair follicle bulge and seed the epidermis to make pigment.

Table 1

Clinical characteristics of vitiligo patients.

Patient No.	Age	Sex	Race	BSA prior to tofacitinib	BSA after tofacitinib treatment	Body site involvement	Tofacitinib treatment duration, months	Vitiligo disease duration, years	Responder status	Previous treatments
1	54	F	Caucasian	10%	4%	Face, torso, arms and hands, legs and feet	10	4	R	nbUVB, topical tacrolimus
2	45	M	Caucasian	28%	24%	Face, neck, torso, arms and hands, legs and feet	8	23	R	Prednisone
3	46	F	Caucasian	39%	24%	Face, neck, torso, arms and hands, legs and feet	11	16	R	nbUVB, topical steroids, pseudocatalase cream, blister grafting
4	55	F	Caucasian	10%	8%	Face, neck, torso, hands, feet	14	24	R	nbUVB, secukinumab
5	45	M	East Indian	2%	2%*	Torso, elbows and hands	14	5	R	nbUVB, topical tacrolimus
6	28	M	Caucasian	7%	7%	Face, neck, arms and hands, legs	3	14	NR	nbUVB, topical steroids, topical tacrolimus
7	47	F	Hispanic	1%	1%	Face, neck, arms and hands, legs Hands, feet	9	18	NR	nbUVB, excimer laser, topical PUVA, topical steroids
8	49	M	Caucasian	4%	4%	Forehead, torso, arms and hands, legs	15	17	NR	nbUVB, topical steroids, topical tacrolimus
9	32	M	Hispanic	6%	6%	Lower forehead, eyelids, perioral, axillae, elbows and hands, lower back, gluteal cleft, feet	4	12	NR	nbUVB, fraxel laser, cryotherapy, topical tacrolimus
10	73	F	Caucasian	100%	100%	Entire body	11	33	NR	nbUVB, PUVA

BSA, body surface area; R, responder; NR, non-responder; nbUVB, narrow band ultraviolet B; PUVA, psoralen with ultraviolet A

Islands of repigmentation, apparent after 12 treatments with nbUVB phototherapy over 4 weeks, did not change the BSA appreciably at this early time point.

Table 2

Clinical course of vitiligo patients responding to treatment

Patient No.	Clinical course
1	Near-complete repigmentation of face, forearms and dorsal hands over 5 months of tofacitinib 5 mg QD followed by recurrence of depigmentation after discontinuation of tofacitinib. Re-treatment with tofacitinib 5 mg QD, starting in late spring, led to repigmentation of the face, forearms and dorsal hands, and the chest, upper back and shoulders over 10 months; sun-protected body sites remained unchanged.
2	Partial repigmentation of the face, lateral and posterior neck, and forearms over 3 months and near-complete repigmentation of the same areas (notably, not the submental chin) as well as islands of repigmentation involving the dorsal hands and lower legs over 8 months of tofacitinib 5 mg BID; sun-protected body sites remained unchanged. Repigmentation maintained while taking tofacitinib during the winter, when sunlight exposure was minimal.
3	Complete repigmentation of the face and significant repigmentation of the torso and extremities over 11 months of tofacitinib 5 mg BID plus nbUVB 150 mJ/cm ² TIW.
4	Near-complete repigmentation of the face over 14 months of tofacitinib 5 mg BID; sun-protected body sites remained unchanged.
5	No repigmentation of the dorsal hands over 1 year of tofacitinib 5–10 mg BID. He wore dark brown makeup on his hands to disguise the white patches. Subsequently, after 12 treatments of concomitant nbUVB hand phototherapy 350 mJ/cm ² over 4 weeks, islands of repigmentation were apparent.

mg, milligrams; QD, daily; BID, twice daily; nbUVB, narrowband UVB; TIW, three times weekly; mJ, millijoules; cm, centimeters