ORIGINAL ARTICLE

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

Lucy Y. Liu, BA,[a] James P. Strassner, BS,[b] Maggi A. Refat, MD,[b] John E. Harris, MD, PhD,[b] and Brett A. King, MD, PhD[c]
New Haven, Connecticut, and Worcester, Massachusetts

Background: Vitiligo is an autoimmune disease in which 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.

Method: 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 narrowband ultraviolet B phototherapy. Suction blister sampling revealed that the autoimmune response was inhibited during treatment in both responding and nonresponding lesions, suggesting that light rather than immunosuppression was primarily required for melanocyte regeneration.

Limitations: Limitations include the small size of the study population, retrospective nature of the study, 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 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. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.05.043.)

Key words: JAK; Janus kinase; narrowband ultraviolet B; nbUVB; phototherapy; ruxolitinib; tofacitinib; vitiligo.

From the Department of Dermatology,[c] Yale University School of Medicine, New Haven,[a] and Department of Dermatology, University of Massachusetts Medical School, Worcester.[b]
Ms Liu and Mr Strassner contributed equally to this article.
Supported by National Center for Advancing Translational Sciences grant UL1-TR001453. Dr Harris is supported by National Institute of Arthritis and Musculoskeletal and Skin Diseases grant AR069114 and a Stiefel Scholar Award from the Dermatology Foundation. Dr King received funding support from The Ranjini and Ajay Poddar Resource Fund for Dermatologic Diseases Research.
Disclosure: Dr King has served on advisory boards or is a consultant for Aclaris Therapeutics, Concert Pharmaceuticals, Eli Lilly and Company, Pfizer, Regeneron Pharmaceuticals, and Roivant Sciences Ltd. Dr Harris has served on advisory boards, as a consultant, or as principal investigator on research agreements with Pfizer, AbbVie, Genzyme/Sanofi, Concert Pharmaceuticals, Stiefel/GSK, Mitsubishi Tanabe Pharma, Novartis, Aclaris Therapeutics, The Expert Institute, Celgene, Biologics MD, and Dermira. Ms Liu and Mr Strassner and Dr Refat have no conflicts of interest to declare.
Accepted for publication May 21, 2017.
Reprints not available from the authors.
Correspondence to: John E. Harris, MD, PhD, Department of Dermatology, University of Massachusetts Medical School, 364 Plantation St, LRB 325, MA 01605. E-mail: john.harris@umassmed.edu. or Brett A. King, MD, PhD, Department of Dermatology, Yale University School of Medicine, PO Box 208059, New Haven, CT 06520. E-mail: brett.king@yale.edu.
Published online August 16, 2017.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2017.05.043

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 interferon gamma (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 1 disease may be effective in the other.[18] Two case reports described successful repigmentation in vitiligo, 1 using tofacitinib, a Janus kinase (JAK) 1/3 inhibitor,[19] and the other using ruxolitinib, a JAK 1/2 inhibitor,[20] presumably via inhibition of IFN-γ signaling in the skin. Recently, an open-label clinical trial reported efficacy of topical ruxolitinib in patients with vitiligo, in particular, for facial involvement.[21]

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

CAPSULE SUMMARY

- Vitiligo is driven by the destruction of melanocytes by T cells, which is inhibited by tofacitinib treatment.
- Janus kinase inhibitors are a promising targeted treatment for vitiligo.
- Combination therapy using tofacitinib plus light exposure may be required for effective responses in vitiligo.

METHODS

This study is a retrospective case series of 10 patients seen between July 2014 and January 2017. Medical records of patients with vitiligo, age 18 years and older, who were 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 initiation of tofacitinib therapy, all patients underwent baseline laboratory evaluation, including a comprehensive metabolic panel, complete blood cell count with differential, fasting lipid panel, screening for tuberculosis with the QuantiFERON-TB Gold test (Cellestis Limited, Melbourne, Australia), and screening for HIV and hepatitis B and C. Body surface area (BSA) of depigmentation was assessed before and at the end of treatment. Serial laboratory monitoring, physical examinations, and review of systems were used to monitor for adverse events.

Suction blister sampling was performed in 1 patient before the start of tofacitinib treatment and again 10 months later to assess changes in T cell recruitment and chemokine expression; this patient had previously responded to tofacitinib but then relapsed after discontinuing treatment.[19] Three sites were selected for sampling: 1 was a site of vitiligo that did not previously respond to treatment with tofacitinib, 1 was a recently active site (featuring confetti depigmentation[22]) that previously responded to tofacitinib, and 1 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 and 15 mm Hg negative pressure and at a constant temperature of 40°C. Once blisters formed, the blister fluid was aspirated through the roof with a 1-mL insulin syringe. Cells in the blister fluid were pelleted at 330 *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 assay (ELISA) for chemokines. None of the blisters were hemorrhagic.

ELISA

Chemokines were assayed using the Human CXLC9/MIG DuoSet ELISA and Human CXCL10/IP-10 DuoSet ELISA (R&D Systems, Minneapolis, MN) per the manufacturer's instructions. Optical densities were measured with a Perkin Elmer EnVision 2102 multilabel reader (Perkin Elmer, Waltham, MA) 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 CD8 (SK1) were used at 1:20 dilution. Anti-human CD3 (OKT3) was used at 1:200 dilution (BioLegend, San Diego, CA) and Fixable Viability Dye eFluor 455UV at 1:1000 (eBioscience, San Diego, CA). Before cell staining of the peripheral blood mononuclear cells (PBMCs), 10^6 PBMCs were treated with desatinib for 30 minutes at 36°C, pelleted, and incubated with Mart-1