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Janus kinase inhibitors may be an effective treatment to reduce skin depigmentation in vitiligo

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ABSTRACT A clinical decision report appraising Rothstein B, Joshipura D, Saraiya A, Abdat R, Ashkar H, Turkowski Y, Sheth V, Huang V, Au SC, Kachuk C, Dumont N, Gottlieb AB, Rosmarin D. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. *J Am Acad Dermatol.* 2017 Jun;76(6):1054-1060.e1. https://doi.org/10.1016/j.jaad.2017.02.049 for a patient with worsening vitiligo.

Keywords: *Vitiligo, Janus kinase inhibitors, skin re-pigmentation*

Clinical Context

Amira Hadad [pseudonym] is a 34-year-old Middle Eastern woman who presented to an outpatient dermatology clinic for a second opinion regarding treatment of vitiligo. Mrs. Hadad's condition has been present for one year and is affecting her face, axilla, arms, and digits with patches of depigmentation ranging from 3 to 6 cm. She has previously tried intramuscular triamcinolone injections and is currently using topical tacrolimus and narrow-band UVB light, which have limited the progression of her disease but have not reversed the depigmentation. Mrs. Hadad works as a model and opportunities are lacking due to her condition. She is embarrassed to go in public and to socialize in her community. She has been proactive in her treatment plans thus far and has completed her own online research regarding cutting-edge therapies, including the use of Janus kinase (JAK) inhibitors. She expressed the desire and ability to afford any opportunities to help with re-pigmentation. She is able to speak and read both English and Arabic, has access to an automobile, has health insurance through her husband's employer, and has the support of her family allowing her to attend regular healthcare appointments and participate in a clinical trial. For these reasons, the treatment team is considering the use of a JAK inhibitor to help her regain pigmentation.

Clinical Question

Can treatment with a Janus kinase inhibitor reverse skin depigmentation in patients with vitiligo?

Research Article

Rothstein B, Joshipura D, Saraiya A, Abdat R, Ashkar H, Turkowski Y, Sheth V, Huang V, Au SC, Kachuk C, Dumont N, Gottlieb AB, Rosmarin D. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. *J Am Acad Dermatol.* 2017 Jun;76(6):1054-1060.e1. https://doi.org/10.1016/j.jaad.2017.02.049.

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Related Literature

A search for relevant studies was conducted using PubMed via the terms "(vitiligo [title]) AND (Janus* or jak)", yielding 19 results. To identify ongoing studies, clinicaltrials.gov was searched using the term "vitiligo" and filtered to include trials "not yet recruiting", "recruiting", "active-not recruiting", and "completed", yielding 86 results. Abstracts of published studies (PubMed) and protocols for ongoing studies (ClinicalTrials.gov) were retrieved, reviewed, and included if they presented primary research of our topic. JAK inhibitors are a progressive treatment for vitiligo, and the evidence for this therapy is limited. High quality randomized controlled trials are lacking; therefore, case studies and observational studies were included in the review.

Of the 19 articles found via PubMed, 13 were rejected (11 did not answer our clinical question and 2 were not primary research). The remaining 6 clinical studies were reviewed.[1-6] The clinicaltrials.gov search resulted in 2 protocols that examined treatment of vitiligo with JAK inhibitors.[7-8]

Several case studies have illustrated the benefits of JAK inhibitors in patients with vitiligo. Vu et al. presented a case of a male patient with alopecia areata, atopic dermatitis and vitiligo who improved with oral tofacitinib.[1] Joshipura, Plotnikova, et al. reported cases of significant repigmentation of the face with topical ruxolitinib 1.5% cream given twice daily with sun exposure, and repigmentation of sun-exposed areas with oral tofacitinib.[2]

Two retrospective studies were reviewed. Liu et al. published a retrospective case series of 10 patients with vitiligo treated with oral tofacitinib illustrating repigmentation in areas with sun-exposure or UVB phototherapy.[3] Gianfaldoni et al. published a multicenter, observational retrospective study examining the efficacy and safety of UVB micro-phototherapy alone and with tofacitinib. Patients who used tofacitinib citrate and UVB micro-phototherapy achieved nearly complete repigmentation of vitiligo lesions with no side-effects.[4] However, the study population was prescribed tofacitinib citrate for treatment of rheumatoid arthritis; as this is a unique patient population, the study was not included for appraisal.

Rothstein et al. published an open-label, proof-of-concept trial of patients with vitiligo using topical ruxolitinib 1.5% cream twice daily. All patients showed significant improvement in their Vitiligo Area Scoring Index (VASI).[5] The study was extended by Joshipura, Alomran, et al. for an additional 32-weeks.[6] The article published by Rothstein et al. was selected for appraisal as the study best answered our clinical question, and the study sample represented our patient.

The clinicaltrials.gov search produced two clinical trials examining topical ruxolitinib in patients with vitiligo. Dr. David Rosmarin at Tufts Medical Center is examining the effects of twice daily topical ruxolitinib 1.5% cream in 12 patients over a 20-week trial. Recruitment has been completed, and no results have been published.[7] Dr. Kathleen Butler at Incyte Corporation is conducting a clinical trial with a more extensive study protocol including 5 treatment arms of topical ruxolitinib with varying strengths and application times. The study has enrolled 157 patients and no results have been published.[8]

Critical Appraisal

Rothstein et al. performed an open-label, non-randomized pilot study examining the use of topical ruxolitinib in 12 patients with vitiligo. Patients applied topical ruxolitinib 1.5% cream twice daily on their vitiligo patches for 20 weeks. The goal of the study was to determine proof of concept. As a non-randomized, non-controlled clinical study, it is level 2 quality determined with SORT criteria.[9]

No details on patient recruitment were included making it challenging to determine selection bias and participation bias. No control group was used; confounding variables may have played a role in the success of the study. The study sample included male and female patients of a wide range of racial backgrounds and age. Our patient, as a 34-year-old Middle Eastern female, would have met criteria for enrollment. In addition, the study patients had similar experiences with vitiligo to our patient: more than 1% body surface affected, progressive vitiligo, vitiligo affecting all areas of the body, and the use of classic therapies with limited success. A wash-out period was used prior to the study, and concurrent vitiligo treatments were not allowed, reducing confounding effects of other treatments on the results. Both stable and progressive vitiligo were included in the study to minimize indication bias; however, patients with regressing vitiligo were not included.

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The primary outcome was the improvement in the VASI (affected body surface area estimated by the use of hand units multiplied by the percentage of depigmentation within each hand unit) at week 20. The secondary outcome was improvement in Vitiligo European Task Force scoring - a validated tool based on extent of disease, staging and spread. The results of the study were assessed using a 95% confidence interval and a p-value of 0.05. The consequence of the small study sample was a low power for the study.

Of the 12 patients who underwent screening, one patient failed to complete laboratory testing and was not screened, one patient dropped-out due to lack of response, and one patient was lost to follow-up. Data from the last recorded visit were used for the 2 patients who dropped-out.

A statistically significant improvement in overall VASI score for all patients was reported. The majority of improvement occurred on the face; four patients had a statistically significant mean improvement in VASI scoring of 76% at week 20 (50% improvement is considered successful). Mild re-pigmentation occurred on the non-acral upper extremities, and no patients showed lower extremity or truncal repigmentation. Based on these results, the effect size for facial repigmentation was mild to moderate and the extremities mild. The earliest response to treatment was at week 4 of the study, while a majority of patients saw repigmentation after 8 weeks of treatment. Adverse effects included erythema (a known side-effect of JAK inhibitors), hyperpigmentation, and transient acne. Laboratory testing was only performed at screening and not repeated at study conclusion due to low risk of a topical formulation. Moving forward, laboratory testing should be completed at the end of the study to better establish risk for future patients.

This was one of the first studies to evaluate a topical JAK inhibitor in a series of patients with vitiligo and provided an important step in collecting preliminary support for the role of topical JAK inhibitors. The study aim was to determine proof of concept. The paper adequately answered this by demonstrating vitiligo repigmentation in all patients. The patient population and patient experience was comparable to that of our patient. The positive therapeutic response and limited adverse reactions makes this an encouraging treatment option.

Limitations include small sample size and study design. There was no control group, no randomization, and no study blinding. Exposure to natural sunlight was not monitored, which may have contributed to vitiligo improvement. One barrier to treatment with JAK inhibitors is cost. The lowest price for 30 pills of oral tofacitinib 10mg is $2,226.31.[10] The topical formulation of ruxolitinib is not yet FDA approved, but the oral version costs $13,856.40 for 60 x 5 mg tablets.[11] The pilot study did not provide any details for a follow-up study, which is important as pilot studies can cause delays in the dissemination of research findings. The study was supported by the AOA Carolyn L. Kuckein Student Research Fellowship and Incyte Corporation; Incyte Corporation is a biopharmaceutical company and produces one drug, ruxolitinib. The extensive ongoing trial found via the ClinicalTrials.gov search is being conducted by Incyte Corporation also.

Clinical Application

Mrs. Hadad came to our team in distress seeking treatment of her vitiligo. Vitiligo treatments are characteristically unsatisfactory due to the autoimmune nature of the disease and the inability to reverse lesions. Mrs. Hadad trialed several vitiligo therapies with minimal success, and she expressed interest in utilizing a JAK inhibitor, leading our team to explore this method of treatment.

We found the evidence for this therapy limited, and the literature search lacking well-controlled randomized studies. Rothstein et al. found a statistically significant improvement in vitiligo for a small sample of patients treated with topical ruxolitinib. The conclusions of this study are promising for a possible application of topical JAK inhibitors in vitiligo, although the sample size was small and financial cost substantial. Given the significant impact of Mrs. Hadad's vitiligo on her career aspirations, her social isolation due to her condition, and her strong motivation to try a new therapy, this treatment could be considered to improve depigmentation. However, after discussion between the patient and our team, it was determined that the benefit of the treatment was unlikely to outweigh the cost at this time. If research of JAK inhibitors continues to progress, this may change.

Two randomized control trials are currently being conducted which will better determine the therapeutic benefits of JAK inhibitors. Although our patient would be eligible to enroll in these studies, they are both no longer actively

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recruiting participants. If a new clinical trial was to begin enrollment, Mrs. Hadad stated she would be interested in participating.

New Knowledge Related to Clinical Decision Science

Vitiligo is challenging to treat and nearly impossible to reverse, causing harmful psychological and social effects. In hopes to improve her condition, our patient wanted to pursue the newest therapies being studied. This critical appraisal explored the clinical decision making associated with the utilization of an innovative therapy and highlighted the importance of researching active clinical trials to provide opportunities for patients to receive these therapies. As found in our case, cutting-edge treatments often lack well-studied evidence and have higher financial expenses. However, in cases where patients are highly motivated, have the economic means, have regular access to healthcare, and the treatment side-effects are low risk (i.e. acne, hyperpigmentation and erythema with topical ruxolitinib), the patient and the physician together may decide to pursue this therapy.

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