ORIGINAL ARTICLE

Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib

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Background: Existing therapies for vitiligo are limited in efficacy and can be associated with undesirable side effects. Topical Janus kinase inhibitors may offer a new therapeutic option for vitiligo.

Objective: We sought to assess the role of topical ruxolitinib 1.5% cream, a Janus kinase inhibitor, in vitiligo treatment.

Methods: This 20-week, open-label, proof-of-concept trial of twice-daily topical ruxolitinib 1.5% cream was conducted in 12 patients with a minimum of 1% affected body surface area of vitiligo. The primary outcome was percent improvement in Vitiligo Area Scoring Index from baseline to week 20.

Results: Of 12 patients screened, 11 were enrolled and 9 completed the study (54.5% men; mean age, 52 years). Four patients with significant facial involvement at baseline had a 76% improvement in facial Vitiligo Area Scoring Index scores at week 20 (95% confidence interval, 53-99%; P = .001). A 23% improvement in overall Vitiligo Area Scoring Index scores was observed in all enrolled patients at week 20 (95% confidence interval, 4-43%; P = .02). Three of 8 patients responded on body surfaces and 1 of 8 patients responded on acral surfaces. Adverse events were minor, including erythema, hyperpigmentation, and transient acne.

Limitations: Limitations of the study include the small sample size and open-label study design.

Conclusions: Topical ruxolitinib 1.5% cream provided significant repigmentation in facial vitiligo and may offer a valuable new treatment for vitiligo. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.02.049.)

Key words: facial vitiligo; Janus kinase inhibitor; ruxolitinib; topical application; VASI; vitiligo.

Vitiligo is an autoimmune disorder in which an acquired loss of functioning melanocytes results in depigmented patches of skin. The often visible, disfiguring lesions of vitiligo have a major impact on patients' quality of life, justifying the need for new therapeutic options. Topical steroids, calcineurin inhibitors, and phototherapy are the mainstay of treatment for vitiligo but are used with limited success.

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Past development of novel therapies for vitiligo was hindered by a lack of knowledge of the underlying immunopathogenic pathway. However, recent chemokine expression profiling performed in human lesional skin has revealed a predominantly T-helper 1–mediated signature with elevated levels of interferon (IFN)-γ and its associated chemokines CXCL9 and CXCL10.[1] In vitiligo mouse models, treatment with neutralizing antibodies of CXCL10 or IFN-γ induced reversal of vitiligo lesions.[1,2] This research highlights the importance of IFN-γ as a driver of vitiligo autoimmunity.

Inhibiting IFN-γ or its downstream effectors such as Janus kinases (JAKs) may be an effective strategy for vitiligo treatment development. JAKs are a family of intracellular nonreceptor tyrosine kinases that are critical for IFN-γ signaling.[3,4] The US Food and Drug Administration–approved JAK inhibitors include ruxolitinib, a JAK1/2 inhibitor approved for the treatment of intermediate- or high-risk myelofibrosis and polycythemia vera, and tofacitinib citrate, a JAK1/3 inhibitor approved for the treatment of moderate-to-severe rheumatoid arthritis. Treatment with oral tofacitinib citrate provided significant repigmentation in a patient with facial and acral vitiligo after approximately 5 months of therapy.[5] Another case report described significant skin repigmentation and hair regrowth in a patient with coexisting facial vitiligo and alopecia areata after a similar duration of therapy with oral ruxolitinib.[6] These case studies support the potential role of JAK inhibition in vitiligo treatment.

In the current phase 2, investigator-initiated, proof-of-concept trial, topical ruxolitinib 1.5% cream was administered to a series of patients with vitiligo for twice-daily use over 20 weeks. The topical form of the drug limits the risk of toxicity associated with systemic use.[7] The primary goal of the study was to determine if topical ruxolitinib use is associated with vitiligo skin repigmentation as determined by significant improvement in the Vitiligo Area Scoring Index (VASI).

CAPSULE SUMMARY

- Existing vitiligo therapies are often limited in efficacy and can be associated with undesirable side effects.
- Topical ruxolitinib 1.5% cream provided a 23% improvement ($P = .02$) in mean Vitiligo Area Severity Index score in 11 patients with vitiligo.
- Topical Janus kinase inhibitors may be beneficial for the treatment of vitiligo.

METHODS

Study design

This open-label, nonrandomized pilot study was conducted at the Tufts Medical Center Department of Dermatology, Boston, Massachusetts. The Tufts University Health Sciences Investigational Review Board approved the study protocol. Baseline laboratory testing (complete blood count, liver function tests, basic metabolic panel, hepatitis B/C panel, and HIV screening) was performed, and no prohibitory abnormalities were observed. Patients with recent vitiligo treatment exposure were required to wash out of treatment within designated time frames (topical treatment, 2 weeks; immunomodulating oral medications, 4 weeks; laser and light treatment, 8 weeks; and investigational/biologic therapies, 12 weeks). Patients were prohibited from using other vitiligo treatments throughout the duration of the trial.

Patients were treated with topical ruxolitinib 1.5% cream for twice-daily use on their vitiligo patches, excluding perioral and periocular areas, for 20 weeks. A minimum of 1% body surface area (BSA) affected by vitiligo was required for inclusion at screening. Topical application of ruxolitinib was limited to 10% BSA, or maximum 3.75 grams per application, to minimize systemic exposure.[7] Patients with greater than 10% affected BSA were limited in their drug application to specific body locations mutually agreed on by the patient and the principal investigator.

Primary and secondary clinical outcomes

The primary outcome was improvement in the VASI at week 20. Multiplication of affected BSA (estimated with the use of hand units) by the degree of depigmentation (0-100%) within each hand unit was performed to calculate a VASI score (possible range, 0-100).[8]

Secondary outcomes included improvement in Vitiligo European Task Force scoring.[9] The Vitiligo European Task Force is a validated tool that grades vitiligo on extent of disease, staging, and spread.[9] Extent of disease is calculated by use of the "rule of nines" to estimate BSA, staging is assessed through degree of depigmentation on a 0 (no depigmentation) to 4 (complete depigmentation) scale, and spread is scored on a simple scale (+1: progressive; 0: stable; −1: regressive). Other secondary outcomes were Physician Global Vitiligo Assessment, BSA, and Dermatology Life Quality Index. Physician Global Vitiligo Assessment was determined by use of a 5-point scale ranging from 0 (clear) to 4 (severe disease).

Abbreviations used:

BSA: body surface area
IFN: interferon
JAK: Janus kinase
VASI: Vitiligo Area Scoring Index

Total BSA was calculated with the use of a handprint (palm plus the volar surface of fingertips) to estimate 1% BSA. Photographs of vitiligo patches were taken at all study visits to help monitor clinical progression.

Statistical analysis

Descriptive statistics were used for primary and secondary end points. Mean, standard deviation, median, minimum, maximum, and 95% confidence intervals (CIs) are provided for continuous variables. A paired *t* test was used with a *P* value of .05 as a cutoff, performed on normalized percentage improvement per patient. Counts, percentages, and 95% CIs were provided for categorical variables. Intention-to-treat analysis was performed, and data from the last recorded visit were used for 2 patients who dropped out.

RESULTS

Patient demographics

Twelve patients (age, 18 years and older) underwent screening. Eleven patients were enrolled, and 9 patients successfully completed 20 weeks of the study. One patient screen failed because of inability to complete the required laboratory testing. Another patient with facial and acral (hand/foot) involvement dropped out of the study after 16 weeks because of lack of response, and 1 who was responding was lost to follow-up after his 8-week visit. Patients were 54% men, with a mean age of 52 years. Four patients had significant facial vitiligo affecting >0.5% BSA of the face (one half of a hand unit) per VASI at baseline. Duration of time since vitiligo onset ranged from 3 to 18 years, with an average of 8.45 years. Four patients had vitiligo that was progressive at their baseline visit, and the remainder had stable disease within the 4 weeks before ruxolitinib initiation. All patients had nonsegmental vitiligo. Past treatments included topical steroids, calcineurin inhibitors, phototherapy, and excimer laser, and 2 patients failed a clinical trial of abatacept biologic therapy.

Patient demographics are listed in Table I. Patient race/ethnicity was classified according to categories (white, black, Hispanic, and other) defined by the investigator.

Table I. Baseline patient demographic and clinical characteristics (n = 11)

Sex, No. (%)	
Male	6 (54.5)
Female	5 (45.5)
Age, mean, [range], y	52 [33-65]
Race/ethnicity, No. (%)	
White	4 (36.4)
Hispanic	4 (36.4)
Asian	2 (18.2)
Other	1 (9.1)
Duration of disease, mean [range], y	8.45 [3-18]
History of thyroid disorder, No. (%)	3 (27)
Previous steroid use, No. (%)*	2 (18.9)
Vitiligo activity, No. (%)†	
Progressive	5 (45.5)
Regressive	0 (0.0)
Stable	6 (54.5)
Vitiligo affecting >0.5% BSA of face, No. (%)	4 (36.4)
Acral vitiligo, No. (%)	8 (72.7)
Nonacral extremity vitiligo, No. (%)	8 (72.7)
Truncal vitiligo, No. (%)	4 (36.4)
VASI, mean (standard deviation), median, [range] %	9.8 (18.3), 2.04, [0.38-63.25]
BSA, mean (standard deviation), median, [range] %	11.05 (19.6), 2.75, [1.0-68.0]

BSA, Body surface area; *VASI*, Vitiligo Area Scoring Index.
*Patients who were using topical steroids on screening but stopped 4 weeks before baseline visit.
†Vitiligo activity in 4 weeks before baseline visit.

Vitiligo Area Scoring Index

Fig 1 demonstrates the improvement in overall VASI score at sites of application of topical ruxolitinib, shown by the percent improvement in VASI score from baseline through week 20. Individual patient improvement is demonstrated in Fig 2. A statistically significant mean percent improvement in overall VASI score of 23% (95% CI, 4-43%; *P* = .02) was observed for all enrolled patients (n = 11), corresponding to a mean VASI score of 9.8 at baseline and 8.9 at week 20. Percent change in individual VASI scoring ranged from 0% to 98%. A percent improvement in overall mean VASI score of 27% (95% CI, 4-50%; *P* = .02) was observed for patients who completed the trial (n = 9).

Eight of 11 patients had some treatment response, although the most significant response consisted of facial repigmentation. Four patients had >0.5% BSA affecting the face (one half of a hand unit) at baseline and had a statistically significant mean improvement in VASI scoring of 76% (95% CI, 53-99%; *P* = .001) at week 20 (Fig 3). The earliest sign of response in the study was at week 4 in 1 patient with facial vitiligo.

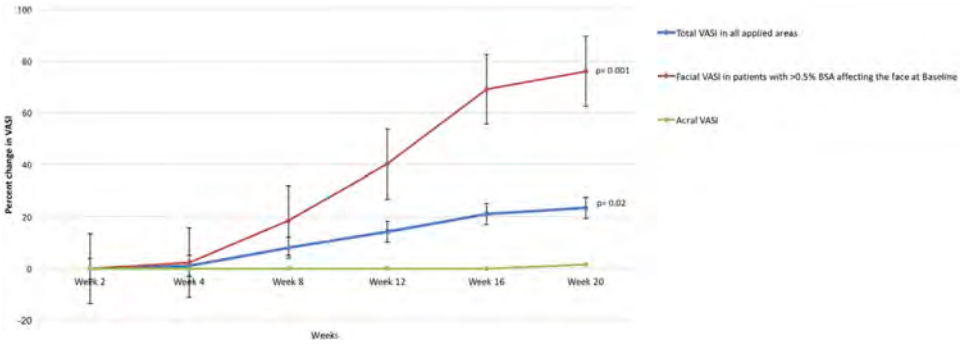

Fig 1. Vitiligo. Percent change (improvement) in Vitiligo Area Scoring Index (VASI) scoring from baseline to week 20 after twice-daily topical ruxolitinib application.

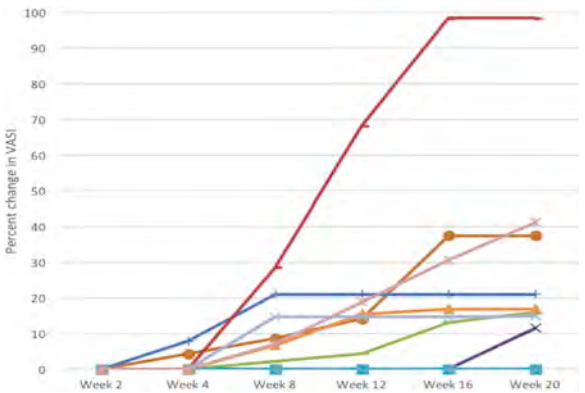

Fig 2. Vitiligo. Individual subject percent change (improvement) in Vitiligo Area Scoring Index scoring from baseline to week 20 after twice-daily topical ruxolitinib application.

However, the majority of patients began to see repigmentation of their facial vitiligo after 8 weeks of treatment. Alhough patients did not apply topical ruxolitinib to their eyelids, 2 patients noted early periocular repigmentation.

Three of 7 patients responded on the nonacral upper extremities. The earliest upper-extremity response was at week 12 for 1 patient and week 20 for 2 additional patients, with an overall minor VASI score improvement of 3.6%. One patient (1/8) with acral involvement at baseline had slight acral repigmentation (9%). No patients had lower-extremity or truncal repigmentation. Ultimately, nonfacial vitiligo showed minor, non−statistically significant clinical improvement. In 3 patients, new vitiligo patches developed in areas not being treated. None of the existing vitiligo patches at baseline worsened. No statistically significant differences in Physician Global Vitiligo Assessment or Dermatology Life Quality Index were observed at week 20 from baseline, but it is likely that the study was not powered enough to detect a change in these parameters.

Vitiligo European Task Force scale

Disease extent was measured with the use of BSA, which underwent a mean percent reduction of 11.2% ± 26.4%, which was not statistically significant (P = .19). Staging, which reflects disease severity, was not statistically significant at week 20, with a mean of 4.8 at baseline and 4.5 at week 20. However, spreading, which indicates progression or regression, showed statistically significant (P = .016) improvement, given repigmentation in 8 of 11 patients at week 20, corresponding to a mean baseline staging score of 0.5 reduced to −0.5 at week 20.

Adverse events

Erythema over the affected lesion was observed in 8 of 11 patients (Fig 4). A rim of hyperpigmentation surrounding the vitiligo patches was observed on facial as well as acral vitiligo patches in 9 of 11 patients (Supplemental Fig 1; available at http://www.jaad.org). Transient papular eruptions or worsening of acne was seen in 2 patients after application of ruxolitinib on facial vitiligo. There were no severe or lasting side effects. Laboratory testing was only performed at screening and was not repeated again because the risk of systemic toxicity was low, given the topical formulation and limited systemic absorption with treatment of less than 10% BSA or less than 3.75 grams of ruxolitinib per application.[7]

DISCUSSION

To our knowledge, this is the first study to evaluate a topical JAK inhibitor, ruxolitinib, in a series of patients with vitiligo. One prior case report documented clinical success with topical ruxolitinib for the treatment of scalp and eyebrow alopecia areata, another T-helper 1−mediated disease.[10] Similar to the general vitiligo population, our study cohort had an almost equal number of male and

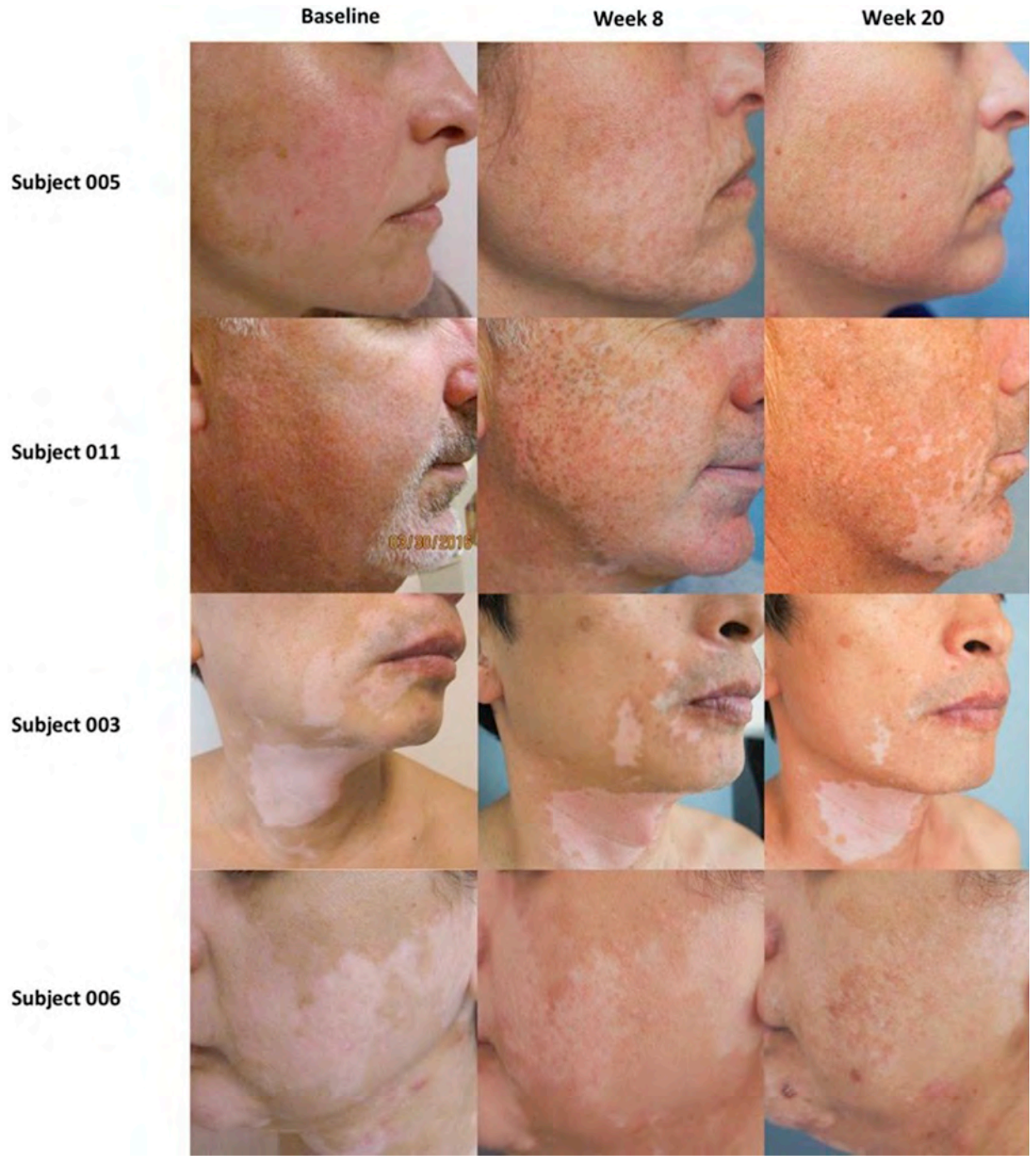

Fig 3. Vitiligo. Significant repigmentation in facial vitiligo after twice-daily topical ruxolitinib application at baseline, week 8, and week 20 in 4 patients who had >0.5% body surface area per Vitiligo Area Scoring Index score of facial involvement at baseline.

female participants, and 3 of 11 patients had a history of other autoimmune conditions including thyroid disease. Most patients previously used conventional vitiligo therapies, with limited success.

The majority of overall VASI score improvement from baseline is composed of facial repigmentation (Fig 1). An approximately 76% improvement in VASI scoring was observed in 4 patients with significant facial vitiligo. A 50% improvement in VASI scoring is considered a clinically successful treatment response.[11] This significant facial repigmentation was observed in patients with varying years of history of vitiligo and in those with active or stable disease at baseline, suggesting

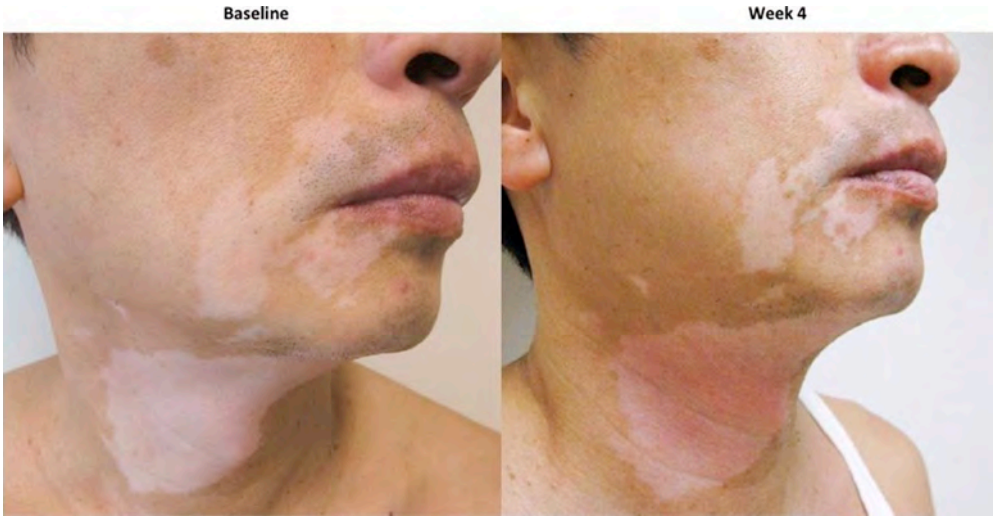

Fig 4. Vitiligo. Earliest sign of vitiligo repigmentation in this cohort of patients occurring on the face of subject 003 at the week 4 visit. Note adverse effect of erythema on the anterior neck.

that disease duration or activity may not be critical in determining response to therapy. In particular, a patient with an 18-year history of vitiligo had facial response to treatment. In addition, the extent of disease involvement did not affect facial vitiligo improvement, because 1 patient with the highest affected BSA at baseline (68%) experienced facial repigmentation.

Vitiligo located on the face responded more robustly to ruxolitinib use compared with other parts of the body. Only 3 of 8 (37.5%) and 1 of 8 (12.5%) patients with vitiligo located on the body (nonacral extremities and trunk) and acral surfaces, respectively, experienced repigmentation, with an overall 0.3% and 1.5% mean percent change in VASI score at week 20, respectively. Acral surfaces tend to be more resistant to other established vitiligo therapies as well.[9,12] We have hypothesized that the thinner epidermis of the face may facilitate more rapid and complete medication absorption, although research has shown that the resistance of acral sites to repigmentation is probably secondary to the lower acral density of pilosebaceous follicles.[12] The face also experiences relatively more sun exposure than the trunk and proximal extremities. Two patients had vitiligo repigmentation on their faces and forearms but not on affected areas concealed from the sun such as the shoulders and trunk. It is possible that the medication effect may be enhanced by sun exposure, but more data are needed to substantiate this finding. Two patients had repigmentation on their untreated eyelids. Given that inflammation in vitiligo is elevated in normal-appearing perilesional skin compared with that in stable lesions, it is possible that ruxolitinib applied to skin adjacent to the eyelids eliminated peripheral inflammation and allowed for periocular repigmentation.[13] Future studies may better help to elucidate the mechanism of this phenomenon.

A possible signal for impending response on the face was an initial hyperpigmented border surrounding vitiligo patches. Nine of 11 patients experienced this effect. This rim of hyperpigmentation initially caused concern for some patients because it manifested before any lesional skin repigmentation. However, for 7 of 11 patients, the border of hyperpigmentation was followed by subsequent repigmentation of facial vitiligo in a peripheral, diffuse, and perifollicular manner. Repigmentation occurred approximately 4 to 6 weeks after the start of hyperpigmentation. The hyperpigmentation resolved as patients' treated skin repigmented.

Erythema on treated skin was the most commonly observed adverse event in 72% of patients, affecting both responders and nonresponders. However, this is a known side effect of the drug that has been observed in prior clinical trials in nonvitiligo subjects. Two patients did experience transient, mild facial acne, with 1 having worsening of pre-existing acne, but this resolved quickly within 1 week and did not return. No adverse events led to study discontinuation. It is unknown whether patients had laboratory changes such as thrombocytopenia, anemia, or neutropenia, which are associated with oral ruxolitinib use, because laboratory monitoring was not performed after baseline.[7] We cannot comment on what occurs when patients stop treatment; however, in 1 report of oral ruxolitinib, the patient rapidly lost response,

and, in patients with alopecia areata, the response was lost.[6]

Limitations of this study include the small sample size and the open-label study design. Natural sun exposure was not monitored in our subjects. The study was conducted in Boston from January through August; thus, natural sunlight could have contributed indirectly to vitiligo improvement. However, the purpose of this proof-of-concept trial was to investigate the early role of topical JAK inhibitors in vitiligo. Even with a small number of patients, we were able to detect a meaningful change in vitiligo repigmentation. Future studies should be aimed at conducting large-scale, randomized, controlled trials to better understand the efficacy and adverse events of topical JAK inhibitors in vitiligo and other T-helper 1–mediated diseases, along with testing higher concentrations of ruxolitinib and its safety in combination with other treatment modalities such as phototherapy.

CONCLUSIONS

Topical JAK inhibition may offer a promising new treatment for vitiligo. Because laboratory monitoring was not performed in our patients, we cannot comment on potential laboratory-adverse events, but it was assumed these were not likely to occur with topical application. Twice-daily application of topical ruxolitinib 1.5% cream produced significant improvement in facial vitiligo in this small cohort of patients. Significant vitiligo repigmentation was observed on the face. Few patients had acral or extremity improvement, and the repigmentation that did occur in these areas was clinically and statistically nonsignificant. However, the encouraging results in facial lesions should prompt further investigation into the role of JAK inhibitors for the treatment of vitiligo.

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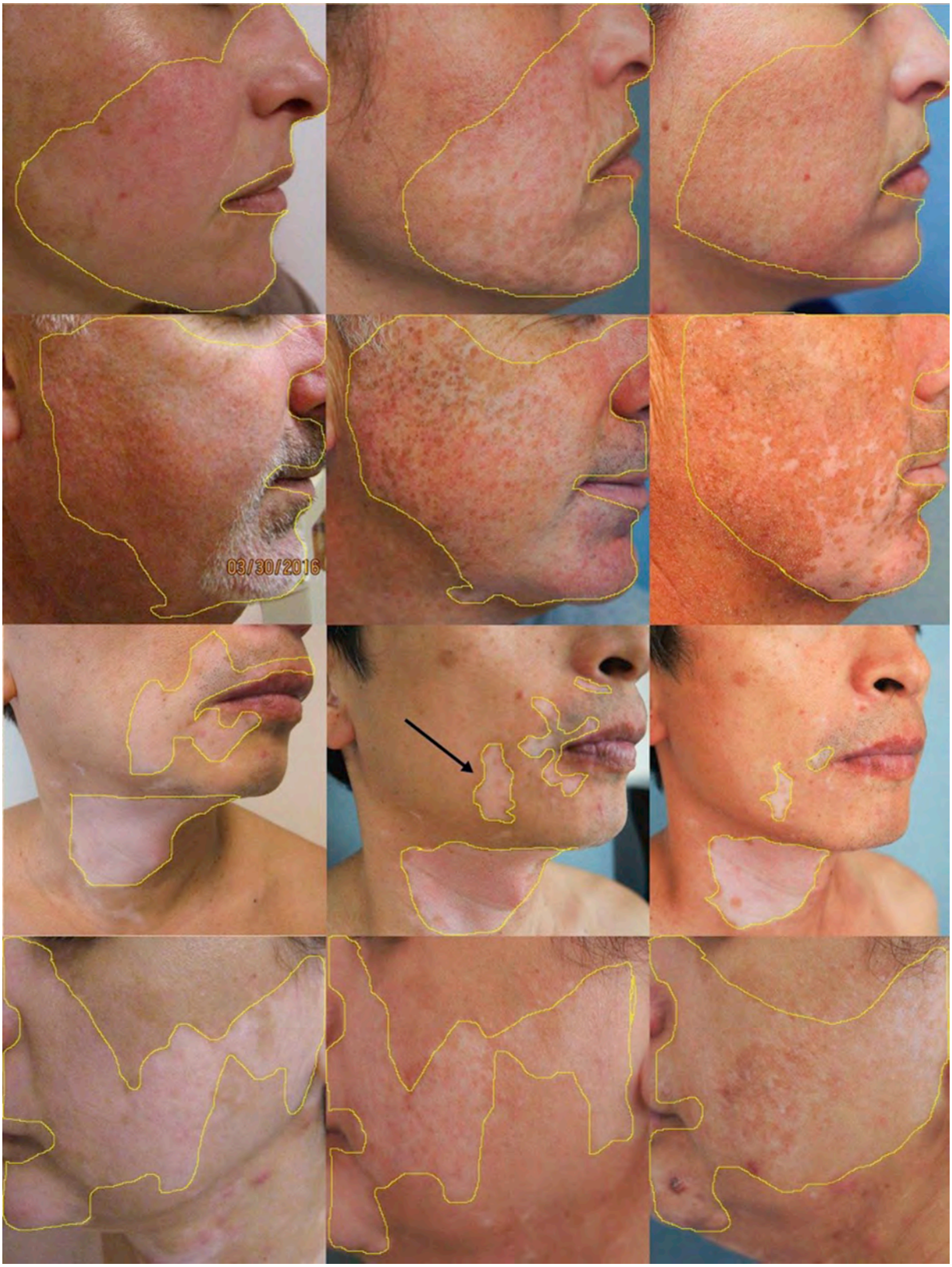

Supplemental Fig 1. Vitiligo. Facial vitiligo repigmentation at baseline, week 8, and week 20 (from left to right), with areas of depigmentation highlighted manually by use of the freehand tool of ImageJ software (National Institutes of Health, Bethesda, MD). *Arrow* points to the hyperpigmented rim observed in several patients.