fortune Journals

Research Article

FORTUNE JOURNAL OF HEALTH SCIENCES

ISSN: 2644-2906

Evaluation of The Safety and Efficacy of Ruxolitinib Cream in The Treatment of Vitiligo- A Comparative Observational Study

Md. Nazmul Haque Sarker*[1], Samia Subreen Shila[2], Kismat Ara Islam[3], Muhammad Humayoun Kabir[4]

Abstract

Background: Vitiligo is a chronic autoimmune disease characterised by depigmented patches of skin that result from the loss of melanocytes. The global prevalence of vitiligo is approximately 0.5–2%, which varies geographically. Patients with vitiligo have a reduced quality of life and often have psychosocial and autoimmune comorbidities. We investigated the therapeutic potential of ruxolitinib cream in patients with vitiligo and report the efficacy and safety results up to 52 weeks of double-blind treatment.

Methods: A comparative observational study was conducted in the department of Dermatology and Venereology, Shaheed Monsur Ali Medical College Hospital, Dhaka, Bangladesh from July to December 2023. All the patients of vitiligo came for treatment at the Department of Dermatology and Venereology in SMAMCH and during this period the patients were studied. Total 100 patients included in our Study. The patients who did not develop enough signs and symptoms of vitiligo were excluded from the study. Patients, investigators, and the study sponsor (except members of the interim analysis and primary endpoint analysis data monitoring teams) remained masked to treatment assignment throughout the study. The primary endpoint was the proportion of patients achieving a 50% or higher improvement from baseline in F-VASI (F-VASI50) at week 24, assessed in the intention-to-treat population.

Results: Total 100 patients were randomly assigned to receive ruxolitinib cream. The mean age was 48·3 years (SD 12·9) and the median age was 49·0 years (range 18–73), 46 (46%) of 100 patients were men and 54 (54%) were women. Most patients (93%) had non-segmental vitiligo and skin types II–III (64%). Median disease duration was 14·0 years (range 0·3–67·9). The mean percentage of T-BSA involvement at baseline was 22·05 (SD 18·38%) and for F-BSA 1·48 (0·86%). The baseline mean T-VASI score was 17·96 (SD 15·45) and the mean F-VASI score was 1·26 (0·82). The reliability and validity of F-VASI and T-VASI instruments as measures of treatment efficacy were confirmed in a post-hoc analysis. Clinically meaningful change was detected for F-VASI with a percentage change of 56% and T-VASI with a percentage change of 42% from baseline, using an approach anchored on the 7-point PaGIC-V scale (appendix pp 30–40). A larger proportion of patients with baseline T-BSA 20% or less who received ruxolitinib cream 1·5% twice daily noted very much or much improvement (scores of 1 or 2) of vitiligo per the PaGIC-V at week 24. Patients who received any dose of ruxolitinib cream showed visible improvement in repigmentation of facial and non-facial vitiligo lesions; repigmentation was most notable with 0.15% once daily and 1·5% twice daily, and patients showed continued improvement up until week 52. All treatment-related adverse events were mild or moderate in severity and similar across treatment groups.

Affiliation:
1Assistant Professor, Department of Dermatology, Shaheed Monsur Ali Medical College, Dhaka, Bangladesh
2Consultant, Department of Laboratory Medicine, Z H Sikder Women's Medical College & Hospital, Bangladesh
3Professor, Department of Dermatology, Shaheed Monsur Ali Medical College, Dhaka, Bangladesh
4Assistant Professor, Department of Respiratory Medicine, Shaheed Monsur Ali Medical College, Dhaka, Bangladesh

***Corresponding author:**
Md. Nazmul Haque Sarker, Assistant Professor, Department of Dermatology, Shaheed Monsur Ali Medical College, Dhaka, Bangladesh

Citation: Nazmul Haque Sarker, Samia Subreen Shila, Kismat Ara Islam, Humayoun Kabir. Evaluation of The Safety and Efficacy of Ruxolitinib Cream in The Treatment of Vitiligo- A Comparative Observational Study. Fortune Journal of Health Sciences. 7 (2024): 574-579.

Received: October 04, 2024
Accepted: October 08, 2024
Published: October 18, 2024

Md. Sarker NH, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.222

Conclusion: In conclusion, study data up until week 52 suggest that ruxolitinib cream monotherapy is an effective treatment option for patients with vitiligo. These data suggest that ruxolitinib cream might be an effective treatment option for patients with vitiligo.

Keywords: Ruxolitinib Cream, Vitiligo, Improvement

Introduction

Vitiligo is a chronic autoimmune disease resulting in skin depigmentation and reduced quality of life. Vitiligo is a chronic autoimmune disease characterised by depigmented patches of skin that result from the loss of melanocytes.[1,2] The global prevalence of vitiligo is approximately 0·5–2%, which varies geographically.[3] Patients with vitiligo have a reduced quality of life and often have psychosocial and autoimmune comorbidities.[4–6] Vitiligo is an autoimmune condition with an estimated prevalence of 0.5%–2% worldwide. [7] Besides the visible cosmetic concerns associated with vitiligo, it is marked by psychological concerns such as anxiety and distress leading to reduced quality of life.[7]The disease is known to be mediated by interferon-gamma (IFN-γ) which acts through the Janus kinase-signal transducer and activator of transcription (JAK–STAT) pathway to recruit CD8+ T cells, which in turn drive the cytotoxicity directed against melanocytes via detachment and apoptosis, leading to the characteristic white skin patches.[7] Ruxolitinib acts as a JAK1 and JAK2 inhibitor to suppress the IFN-γ-mediated pathway and prevent melanocyte damage, allowing them to heal and re-pigment.[8] This meta-analysis aims to systematically collate outcomes from the relatively limited data available and evaluate the efficacy and safety of ruxolitinib in vitiligo patients Vitiligo is caused by the infiltration of affected areas with activated melanocyte antigen-specific CD8+T cells that drive cytotoxicity and disease pathogenesis.[2] Recruitment of autoreactive CD8+T cells to melanocytes is mediated by interferon γ (IFNγ) through the IFNγ-induced chemo- kines C-X-C motif chemokine ligand (CXCL) 9 and 10, a signalling pathway regulated by Janus kinase (JAK) 1 and 2.7–9 CXCL9 and CXCL10 have been validated as biomarkers of vitiligo activity; the concentration of both these factors are increased in the skin and blood of patients with vitiligo compared with healthy controls, and in patients with active versus stable vitiligo.[9-12] Ruxolitinib cream is a topical formulation of the active substance ruxolitinib. Ruxolitinib works as a selective inhibitor by blocking the proteins which are involved in the downstream signalling of the immune system. Preventing the binding of these proteins reduces the immune response. If licensed, administered topically, ruxolitinib cream would offer a pharmacological treatment for patients with vitiligo who currently rely on non-specific and/or unlicensed medicines to treat their condition. Thus, topical administration of a JAK inhibitor is a rational approach to diminish local inflammation and facilitate endogenous repigmentation in patients with vitiligo.

Materials and Methods

A comparative observational study was conducted in the department of Dermatology and Venereology, Shaheed Monsur Ali Medical College Hospital, Dhaka, Bangladesh from July to December 2023. All the patients of vitiligo came for treatment at the Department of Dermatology and Venereology in SMAMCH and during this period the patients were studied. The patients who did not develop enough signs and symptoms of vitiligo were excluded from the study.

The study used an interactive response technology system for the management of study enrolment. The system assigned the patient study numbers, tracked patient visits, randomised according to defined parameters, and maintained treatment masking. The system used a configurable stratification algorithm with limits set to patient age (≤30 and >30 years). Patients were randomly assigned to one dose strengths of ruxolitinib cream 1·5% mg and 0·5% mg. Patients who received ruxolitinib cream once daily also received vehicle cream once daily to maintain masking. Patients, investigators, and the study sponsor (except members of the interim analysis and primary endpoint analysis data monitoring teams) remained masked to each patient's treatment assignment throughout the study. Emergency unmasking could occur if an adverse event required the investigator to learn the patient's treatment assignment. The study was carried out by recording the patients age, sex and duration of diseases. In this sociodemographic study, occupation of patients, family history, life living status, food habits and social problem were recorded.

Statistical analysis: Data are analyzed as Mean±Standard Deviation (SD). Kolmogorov-Smirnov test was used to determine normality of the data. Data with Abnormal distribution were converted to normal distribution by calculating logarithmic ratio. Then data at the end of study were compared to their own baseline values by Paired t-test. Comparison quantitative and qualitative variables between two groups were performed by Student's t-test and exact fisher test, respectively. SPSS version 23 (IBM Inc, USA) was used for data statistical analyses. The $p<0.05$ was considered significance for all variables.

Results

Between July 2023 to December 2023, 100 patients were randomly assigned to receive ruxolitinib cream. The mean age was 48·3 years (SD 12·9) and the median age was 49·0 years (range 18–73), 46 (46%) of 100 patients were men and 54 (54%) were women. The distribution of baseline disease characteristics was similar across treatment groups (table-1).

Md. Sarker NH, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.222

Most patients (93%) had non-segmental vitiligo and skin types II–III (64%). Median disease duration was 14·0 years (range 0·3–67·9). The mean percentage of T-BSA involvement at baseline was 22·05 (SD 18·38%) and for F-BSA 1·48 (0·86%). The baseline mean T-VASI score was 17·96 (SD 15·45) and the mean F-VASI score was 1·26 (0·82).

Table 1: Baseline characteristics (N=100)

Variables	Ruxolitinib cream		
	0·15% once daily group (n=50)	1·5% twice daily group (n=50)	Total (n=100)
Age, years	45·1 (11·5)	49·5 (12·3)	48·3 (12·9)
≤30	5 (10%)	5 (10%)	10 (10%)
>30	45 (90%)	45 (90%)	90 (90%)
Sex			
Male	20 (40%)	26 (52%)	46 (46%)
Female	30 (60%)	24 (48%)	54 (54%)
Baseline F-VASI	1·19 (0·75)	1·26 (0·81)	1·26 (0·82)
Baseline T-VASI	14·57 (9·05)	16·94 (14·26)	17·96 (15·45)
Facial BSA	1·35 (0·86)	1·55 (0·89)	1·48 (0·86)
Total BSA	17·56 (10·93)	21·46 (16·82)	22·05 (18·38)
Duration of disease, years	13·7 (0·3–67·9)	13·5 (0·8–47·8)	14·0 (0·3–67·9)
Diagnosed in childhood	7 (23%)	10 (30%)	35 (22%)
Type of vitiligo			
Segmental	3 (6%)	4 (8%)	7 (7%)
Non-segmental	45(90%)	48 (96%)	93 (93%)
Disease stability			
Progressive	28 (56%)	29 (58%)	57 (57%)
Stable	21 (42%)	22 (44%)	43 (43%)

Table 2: Skin type of patients with vitiligo (N=100)

Skin type	0·15% once daily group (n=50)	1·5% twice daily group (n=50)	Total (n=100)
I	2 (4%)	2 (4%)	4 (4%)
II	15 (30%)	17 (34%)	32 (32%)
III	13 (26%)	19 (38%)	32 (32%)
IV	13 (26%)	7 (14%)	20 (20%)
V	4 (8%)	2 (4%)	6 (6%)
VI	0	6 (12%)	6 (6%)

Table 3: Other autoimmune disorders and Previous therapy (N=100)

Other autoimmune disorders	0·15% once daily group (n=50)	1·5% twice daily group (n=50)	Total (n=100)
Thyroid disorders	11 (22%)	14 (28%)	25 (25%)
Juvenile diabetes	0	1 (2%)	1 (1%)
Pernicious anaemia	0	0	0 (0%)
Previous therapy	-	-	-
Topical corticosteroids	26 (52%)	20 (40%)	46 (46%)
Calcineurin inhibitors	22 (44%)	23 (46%)	45 (45%)
Phototherapy	10 (20%)	25 (50%)	35 (35%)
Excimer laser therapy	6 (12%)	7 (14%)	13 (13%)
Photochemotherapy	2 (4%)	6 (12%)	8 (8%)
Vitamin D derivatives	2 (4%)	2 (4%)	4 (4%)
Surgical techniques	0	1 (2%)	1 (1%)
Other	6 (12%)	5 (10%)	11 (11%)

The primary endpoint, week 24 F-VASI50, was reached by significantly more patients given the two highest doses of ruxolitinib cream (1·5% twice daily, 15 [30%] of 50 patients, odds ratio [OR] 24·7, 95% CI 3·3–1121·4; p=0·0001; 0.15% once daily, 25 [50%] of 50 patients, OR 28·5, 95% CI 3·7–1305·2; p<0·0001). The reliability and validity of F-VASI and T-VASI instruments as measures of treatment efficacy were confirmed in a post-hoc analysis. Clinically meaningful change was detected for F-VASI with a percentage change of 56% and T-VASI with a percentage change of 42% from baseline, using an approach anchored on the 7-point PaGIC-V scale (appendix pp 30–40). A larger proportion of patients with baseline T-BSA 20% or less who received ruxolitinib cream 1·5% twice daily noted very much or much improvement (scores of 1 or 2) of vitiligo per the PaGIC-V at week 24. Patients who received any dose of ruxolitinib cream showed visible improvement in repigmentation of facial and non-facial vitiligo lesions; repigmentation was most notable with 0.15% once daily and 1·5% twice daily, and patients showed continued improvement up until week 52.

The occurrences and types of treatment-emergent adverse events were similar across treatment groups. Four patients had serious treatment-emergent adverse events (1·5% twice daily, subdural haematoma [n=1]; 1·5% twice daily, seizure [n=1]; 0·15% once daily, coronary artery occlusion [n=1] and oesophageal achalasia [n=1]) unrelated to study treatment. Application site pruritus was the most common treatment-related adverse event among patients given ruxolitinib cream (1·5% twice daily, one [2%] of 50; 0.15% once daily, 3[6%]

Md. Sarker NH, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.222

of 50; 0·15% once daily, 6 [12%] of 50). Acne was noted as a treatment-related adverse event in 6 (12%) of 100 patients who received ruxolitinib cream. All treatment- related adverse events were mild (grade 1) or moderate (grade 2) in severity. Three patients had a treatment- emergent adverse event leading to treatment discontinuation (0·15% once daily and vehicle [both n=1], headache [related to treatment for 0·15% once daily]; 1·5% twice daily [n=1], seizure). At week 52, haemoglobin and platelet concentrations were generally similar to those observed at baseline. Ruxolitinib cream bioavailability was limited, corresponding to approximately 4–7% of the topical dose applied. VASI assessment and monitoring of adverse events were done at baseline and at weeks 4, 8, 12, 18, 24, 28, 34, 40, 46, and 52 (or end of treatment or upon early termination). Patient's Global Vitiligo Assessment (PaGVA), Physician's GVA (PhGVA), and Patient Global Impression of Change– Vitiligo (PaGIC-V) were administered at baseline and weeks 12, 24, 40, and 52.

Table 4: Treatment-emergent adverse events up to 52 weeks of treatment

Treatment-emergent adverse	0·15% once daily group (n=50)	1·5% twice daily group (n=50)
Patients with treatment-emergent adverse	32 (64%)	35 (70%)
Most common treatment-emergent adverse events		
Acne	6 (12%)	9 (18%)
Viral upper respiratory tract infection	5 (10%)	1 (2%)
Application site pruritus	9 (18%)	1 (2%)
Pruritus	1 (2%)	4 (8%)
Upper respiratory tract infection	1 (2%)	4 (8%)
Headache	1 (2%)	2 (4%)
Sinusitis	2 (4%)	2 (4%)
Patients with treatment-related adverse events	17 (34%)	15 (30%)
Most common treatment-related adverse events		
Application site pruritus	9 (18%)	1 (2%)
Acne	1 (2%)	9 (18%)
Pruritus	1 (2%)	2 (64%)
Patients with treatment-emergent adverse events leading to discontinuation	1 (2%)	0
Patients with serious treatment-emergent adverse events	0	1 (2%)

Discussion

Vitiligo is the most common disorder of depigmentation, and in 2012 its worldwide prevalence ranged from 0.06-2.28%.[13,14] It is characterized by the absence of pigment in the skin, secondary to the loss of melanocytes.[13,15] Melanocytes are found in several tissues in the skin, hair follicles, eyes, inner ear, bones, heart and brain.[16] Melanocytes are found in the basal layer of the epidermis and together with the surrounding keratinocytes form the epidermal unit, whose main function is to produce and distribute melanin by a complex process called melanogenesis. [16-19] As Vitiligo become a social problem in Bangladesh, Therefore the social awareness about the Vitiligo, it is essential to sociodemographic studies on Vitiligo in Bangladesh. In this present study, 100 Vitiligo patients were studied simultaneously. The patient's number is not so small but this study reflected various sociodemographic characteristic of Vitiligo patients in Bangladesh. The mean age was 48.3 years (SD 12.9) and the median age was 49.0 years (range 18–73), 46 (46%) of 100 patients were men and 54 (54%) were women. The distribution of baseline disease characteristics was similar across treatment groups. This results complies reported that 40-50% patients developed Vitiligo at the age of 10 to 20 years. Continuous improvement was seen following 52 weeks of ruxolitinib cream monotherapy, with 1·5% twice daily producing the highest responses in F-VASI50 (58%), F-VASI75 (52%), and F-VASI90 (32%). Responses for F-VASI75 and F-VASI90 approximate desired patient outcomes of complete or near-complete repigmentation;[20] these responses paralleled improvements in PhGVA and PaGVA scores at week 52. Although not quantitatively assessed, clinical images of patients with substantial VASI improvement showed favourable subjective appearance of repigmentation. Additionally, ruxolitinib cream was well tolerated, as occurrences and types of treatment-emergent adverse events were generally similar across ruxolitinib cream. Acne was more common in patients who received ruxolitinib cream and will be further assessed in phase 3 studies. Four serious treatment emergent adverse events were observed, but all were deemed unrelated to treatment. All treatment-related adverse events were mild or moderate in severity. Long-term use of topical corticosteroids is associated with skin atrophy,[21] and calcineurin inhibitors are associated with local reactions (eg, burning).[22] In contrast to other topical therapies, the results of this study indicate a low frequency of application site reactions after treatment with ruxolitinib cream. Because keratino-cytes are the primary producers of chemokines that promote vitiligo pathogenesis,[23] targeting the local immune response with a topical treatment provides directed therapy with few systemic adverse effects. Because the IFNγ pathway is central to vitiligo pathogenesis, [23,24] the reduction of IFNγ–mediated biomarkers with topical application of ruxolitinib

Md. Sarker NH, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.222

suggests the potential for disease disruption. Specifically, ruxolitinib cream treatment was associated with significant reductions in circulating concentrations of CXCL10, which primarily recruits CD8T cells to the site of inflammation; CCL18, an inflammatory chemokine associated with inflammation in several dermatoses; and soluble CD27, a T-cell costimulatory molecule that promotes IFNγ signalling. These observations suggest that longer duration treatment with ruxolitinib cream and the resulting repigmentation are associated with decreased keratinocyte-mediated inflammation and the subsequent release of skin-associated inflammatory mediators into circulation. Our findings are consistent with those of earlier work showing that treatment of vitiligo reduced serum CXCL10 concentrations and the reduction occurred in parallel with disease stabilisation. [10] At 24 weeks, although clinical markers of efficacy (eg, F-VASI50) indicated similar improvement with 1·5% twice daily and 0.15% once daily administration, the chemokine profile showed maximal serum CXCL10 reduction with 1·5% twice daily. By week 52, clinical markers of efficacy showed maximal responses with 1·5% twice daily. Vitiligo therapy is a two- step process: arrest of immune autoreactivity followed by melanocyte recruitment,[25] with a time lag between these events before a clinical effect can be realised. As such, longer duration therapy seems to have allowed for clinical effect to more closely reflect altered IFNγ–mediated pathogenesis. Study limitations included that most patients were older than 30 years and had fairer skin types (ie, skin types I–III). There were small numbers of patients in each group, so confirmation of these findings in a larger patient population is needed. Quality of life was not assessed in this phase 2 study and should be explored in future analyses. Finally, additional analyses are needed to further elucidate any correlation between circulating chemokines and the number and function of skin-associated T cells, as well as changes in the skin chemokine concentrations.

Conclusion

In conclusion, study data up until week 52 suggest that ruxolitinib cream monotherapy is an effective treatment option for patients with vitiligo. The reduction of serum CXCL10 suggests that ruxolitinib might work by altering some of the key pathways involved in vitiligo pathogenesis. Longer duration therapy seems to be required for repigmentation, as objectively assessed using the VASI (ie, near-complete facial repigmentation as assessed by F-VASI75 and substantial total body repigmentation as assessed by T-VASI50); this finding is also supported by trends in the PhGVA and PaGVA data at week 52.

References

1. Taïeb A, Picardo M. Clinical practice. Vitiligo. N Engl J Med 360 (2009): 160–69.
2. van den Boorn JG, Konijnenberg D, Dellemijn TA, et al. Autoimmune destruction of skin melanocytes by perilesional T cells from vitiligo patients. J Invest Dermatol 129 (2009): 2220–32.
3. Kruger C, Schallreuter KU. A review of the worldwide prevalence of vitiligo in children/adolescents and adults. Int J Dermatol 51 (2012): 1206–12.
4. Morrison B, Burden-Teh E, Batchelor JM, Mead E, Grindlay D, Ratib S. Quality of life in people with vitiligo: a systematic review and meta-analysis. Br J Dermatol 177 (2017): e338–39.
5. Patel KR, Singam V, Rastogi S, Lee HH, Silverberg NB, Silverberg JI. Association of vitiligo with hospitalization for mental health disorders in US adults. J Eur Acad Dermatol Venereol 33 (2019): 191–97.
6. Sheth VM, Guo Y, Qureshi AA. Comorbidities associated with vitiligo: a ten-year retrospective study. Dermatology 227 (2013): 311–15.
7. Bergqvist C, Ezzedine K. Vitiligo: a review. Dermatology 236 (2020): 571-592.
8. Rosmarin D, Pandya AG, Lebwohl M, et al. Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial. Lancet 396 (2020): 110-120.
9. Abdallah M, El-Mofty M, Anbar T, et al. CXCL-10 and interleukin-6 are reliable serum markers for vitiligo activity: a multicenter cross- sectional study. Pigment Cell Melanoma Res 31 (2018): 330–36.
10. Wang XX, Wang QQ, Wu JQ, et al. Increased expression of CXCR3 and its ligands in patients with vitiligo and CXCL10 as a potential clinical marker for vitiligo. Br J Dermatol 174 (2016): 1318–26.
11. Strassner JP, Rashighi M, Ahmed Refat M, Richmond JM, Harris JE. Suction blistering the lesional skin of vitiligo patients reveals useful biomarkers of disease activity. J Am Acad Dermatol 76 (2017): 847–55.
12. Zhang L, Chen S, Kang Y, et al. Association of clinical markers with disease progression in patients with vitiligo from China. JAMA Dermatol 156 (2020): 288–95.
13. Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. Lancet 386 (2015): 74–84.
14. Krüger C, Schallreuter KU. A review of the worldwide prevalence of vitiligo in children/adolescents and adults. Int J Dermatol 51 (2012): 1206–1212.
15. Gauthier Y, Cario Andre M, Taïeb A. A critical appraisal of vitiligo etiologic theories. Is melanocyte loss a melanocytorrhagy? Pigment Cell Res 16 (2003): 322–332.

Md. Sarker NH, et al., Fortune J Health Sci 2024
DOI:10.26502/fjhs.222

16. D'Mello SA, Finlay GJ, Baguley BC, Askarian-Amiri ME. Signaling pathways in melanogenesis. Int J Mol Sci 17 (2016).

17. Videira IF, Moura DF, Magina S. Mechanisms regulating melanogenesis. An Bras Dermatol 88 (2013): 76–83.

18. Costin GE, Hearing VJ. Human skin pigmentation: Melanocytes modulate skin color in response to stress. FASEB J 21 (2007): 976–994.

19. Hara M, Toyoda M, Yaar M, Bhawan J, Avila EM, Penner IR, Gilchrest BA. Innervation of melanocytes in human skin. J Exp Med 184 (1996): 1385–1395.

20. Eleftheriadou V, Hamzavi I, Pandya AG, et al. International Initiative for Outcomes (INFO) for vitiligo: workshops with patients with vitiligo on repigmentation. Br J Dermatol 180 (2019): 574–79.

21. Njoo MD, Spuls PI, Bos JD, Westerhof W, Bossuyt PMM. Nonsurgical repigmentation therapies in vitiligo: meta-analysis of the literature. Arch Dermatol 134 (1998): 1532–40.

22. Lee JH, Kwon HS, Jung HM, et al. Treatment outcomes of topical calcineurin inhibitor therapy for patients with vitiligo: a systematic review and meta-analysis. JAMA Dermatol 155 (2019): 929–38.

23. Richmond JM, Bangari DS, Essien KI, et al. Keratinocyte-derived chemokines orchestrate T-cell positioning in the epidermis during vitiligo and may serve as biomarkers of disease. J Invest Dermatol 137 (2017): 350–58.

24. Rashighi M, Harris JE. Interfering with the IFN-γ/CXCL10 pathway to develop new targeted treatments for vitiligo. Ann Transl Med 3 (2015): 343.

25. Joshipura D, Plotnikova N, Goldminz A, et al. Importance of light in the treatment of vitiligo with JAK-inhibitors. J Dermatolog Treat 29 (2018): 98–99.