Topical Ruxolitinib cream for refractory cutaneous Dermatomyositis:
PART 1: Prospective, Single-Arm, Open-Label Pilot study

Anthony P. Fernandez, MD, PhD
Cleveland Clinic, Cleveland, Ohio

Dermatomyositis (DM) is an immune-mediated disease that most commonly affects the skin and the muscles. Cutaneous involvement of DM can lead to ulceration with secondary infection, in addition to permanent skin damage in the form of atrophy, scarring, calcinosis, decreased range of motion or lipoatrophy. Furthermore, persistent cutaneous DM is associated with adverse psychological effects and physical symptoms such as pain, burning, and pruritus. The combination of these contribute to a significant negative impact on DM patients' quality of life (**1**). Thus, effective treatment of cutaneous DM represents an important therapeutic goal (**2**).

Unfortunately, cutaneous DM manifestations often persist despite myositis resolution and can be particularly difficult to control. Studies in patients with juvenile DM have found that up to 60% have persistent rash, and the percentage with persistent rash is often more than double that of patients with persistent myositis (**3-5**). In a recent study of adult DM patients who were prospectively observed, only 28 of 74 (38%) achieved clinical remission of their cutaneous disease over a 3-year period despite aggressive systemic therapy treatment regimens (**6**).

Given its refractory nature, combination systemic therapy is often prescribed in attempts to control DM skin involvement, including systemic glucocorticoids, antimalarials and various steroid-sparing immunosuppressive medications. Despite such combinations, though, cutaneous manifestations of DM still often remain refractory and symptomatic. In these patients, in particular, lack of adequate skin improvement coupled with increased risk of serious infection or malignancy from systemic immunosuppression becomes concerning. Therefore, safe and effective treatments for cutaneous disease represents an unmet need for patients with DM.

Janus kinase inhibitors (JAK inhibitors) are a relatively new class of medications that have been hypothesized to have utility in treating various autoimmune diseases, including DM (**7, 8**). Excitement for the emerging use of JAK inhibitors in patients with DM has been underscored by their efficacy in case reports and small trials. Specifically, oral ruxolitinib and tofacitinib have recently been reported to effectively treat DM patients, all of whom had refractory cutaneous disease despite previous or current exposure to numerous systemic medications (**9-11**). However, adding further systemic immunosuppression to DM patients who are otherwise controlled except for refractory skin disease is unattractive due to risk of infection, and other possible adverse effects of oral JAK inhibitors may preclude their use in some DM patients.

The addition of topical corticosteroids and calcineurin inhibitors for refractory DM skin involvement as adjunct treatment in patients already taking systemic medications is attractive because they do not lead to further immunosuppression. However, cutaneous DM symptoms and inflammation are also often refractory to these topical medications (**12, 13**). Additionally,

continued topical corticosteroid use is associated with well-known adverse effects, including potential worsening of DM-related skin atrophy and adrenal insufficiency (**14, 15**).

Recently, topical ruxolitinib has been developed and studied in several dermatologic conditions. In phase 2 and 3 trials in atopic dermatitis, topical ruxolitinib 1.5% cream resulted in significant efficacy in terms of improving both disease activity and itching, without significant side effects (**16-18**). We propose to study use of topical ruxolitinib 1.5% cream as an adjunct for treatment of refractory cutaneous DM lesions in patients who have previously failed other topical medication options.

Study Design (PART 1)

Prospective, Single-Arm, Open-Label Pilot study

Patient population and estimated sample size:

I. Approximately **15-30** patients with refractory cutaneous symptoms (**CDASI activity score ≥6**) related to either classic dermatomyositis, juvenile dermatomyositis, or amyopathic dermatomyositis will be enrolled.
   a. 15 patients are need to detect a 35% decrease in the mean CDASI activity score or CDASI total score with 80% power and significance level of 0.05 at 8 weeks.
   b. 20 patients are need to detect a 30% decrease in the mean CDASI activity score or CDASI total score with 80% power and significance level of 0.05 at 8 weeks.
   c. 29 patients are need to detect a 25% decrease in the mean CDASI activity score or CDASI total score with 80% power and significance level of 0.05 at 8 weeks.

Inclusion Criteria:

- Patients 18 years and older with refractory cutaneous symptoms related to either classic dermatomyositis (CD), juvenile dermatomyositis (JD), or amyopathic dermatomyositis (AD). Diagnosis will be based on either Bohan and Peter criteria (CD and JD) or Sontheimer's criteria (AD) (**19-22**).

- Patients must have had a skin biopsy with histologic features consistent with dermatomyositis and current cutaneous manifestations consistent with dermatomyositis.

- Patients will be considered to have refractory disease if cutaneous manifestations exist despite treatment with systemic corticosteroids and at least one steroid-sparing systemic treatment commonly found to be useful in patients with dermatomyositis. These may include azathioprine, cyclosporine, mycophenolate mofetil, IVIG, methotrexate, hydroxychloroquine, cyclophosphamide, chlorambucil, sirolimus, tacrolimus, and rituximab.

- Patients must have sufficiently active cutaneous involvement of dermatomyositis (**BSA≥1% to ≤20%, CDASI activity score ≥ 6, and Physician Global Assessment (PGA) activity score ≥2**).

- Patients must have tried and failed at least one commonly prescribed **topical medication** in the past, with the last application of a topical medication to active skin lesions occurring greater than 2 weeks prior to enrollment.
    - Commonly prescribed topical medications for dermatomyositis include corticosteroids or calcineurin inhibitors (tacrolimus or pimecrolimus).

- Patients must have been on a stable systemic medication regimen for at least 2 months (60 days) and must agree to keep the regimen stable throughout the study period. As patients with dermatomyositis are commonly treated with combination regimens that include both topical and systemic immunosuppressive medications, any added risk of adverse effects related to ruxolitinib 1.5% cream is considered negligible.

- Patients must be agreeable to use appropriate contraceptive measures while enrolled in the study.
    - Women of childbearing potential must be willing to practice abstinence or use either an oral contraceptive medication or IUD if sexually active.
    - Women of childbearing potential must be willing to have monthly urine pregnancy tests while enrolled in the study
    - Men of childbearing potential must be willing to practice abstinence or use condoms if sexually active.

Exclusion criteria:

- Patients with dermatomyositis who have minimal-to-no active cutaneous disease (mild involvement with < 1% total body surface area involved and/or CDASI activity score of < 6).

- Patients who have > 20% total BSA involvement of cutaneous dermatomyositis.

- Patients who have used a common prescription topical medication within the previous 2 weeks.

- Patients whose cutaneous findings are not consistent with dermatomyositis and/or have previous biopsy results suggestive of an alternative diagnosis

- Patients not on stable systemic medication regimens for at least **2** months and/or who will not agree to keep the regimen stable throughout the study period.

- Patients who have previously taken a systemic Janus kinase inhibitor but had a poor response, patients who are currently taking systemic Janus kinase inhibitors, or patients who have used a topical Janus kinase inhibitor for their dermatomyositis or any other condition and had poor responses.

- Patients with inflammatory myositis other than dermatomyositis, such as polymyositis or inclusion body myositis.

- Patients with clear features of an overlap autoimmune myositis or with an inflammatory myositis not consistent with dermatomyositis, such as polymyositis or inclusion body myositis.

- Patients with an active malignancy other than non-melanoma skin cancer, or with malignancy-associated dermatomyositis.

- Patients younger than 18 years old

- Participants with concurrent conditions and history of other diseases:

    a. Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome, Wiskott-Aldrich syndrome).
    b. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before baseline.
    c. Active acute bacterial, fungal, or viral skin infection (eg, herpes simplex, herpes zoster, chicken pox) within 1 week before baseline.
    d. Any other concomitant skin disorder (eg, generalized erythroderma such as Netherton syndrome), pigmentation, or extensive scarring that, in the opinion of the investigator, may interfere with the evaluation of AD lesions or compromise participant safety.
    e. Current or history of hepatitis B or C virus infection

- Pregnant or lactating females, or female patients planning to get pregnant within the study period timeline.

- Patients who are sexually active and/or of child-bearing potential who are unwilling to use appropriate contraceptive measures during the study period.

- Patients with a history of myocardial infarction or major thromboembolic events, including pulmonary embolism, deep venous thrombosis, or ischemic stroke.

- Patients with a history of significant cytopenias.

- Patients with any medical condition that is felt by the primary investigator to place the patient at unreasonable risk for adverse effects during treatment with Ruxolitinib cream.

- Hypersensitivity to ruxolitinib cream or any of its components.

Methods:

I. Patients will be prescribed 1.5% ruxolitinib cream and will be instructed to apply a thin film twice daily to all areas with active cutaneous disease (up to 20% BSA total). All other topical medications used up to this point will be discontinued.

II. Patients will require **follow-up visits in person at 4 weeks, 8 weeks** (*primary endpoint*)**, and 12 weeks (+/- 5 days)** after enrollment, at which time examinations and clinical scoring tool assessments will be repeated.

III. Objective cutaneous DM scoring by the primary investigator at each visit will include the **Cutaneous Dermatomyositis Disease Area and Severity Index** (CDASI) score, **Physician Global Assessment** for (a) **skin activity** (b) **skin damage**, and **estimate of body surface area (BSA) involvement** with active dermatomyositis (**23-28**).

IV. Objective scoring tools to be completed by the patient at each visit will include: **Patient Global Skin Score**, **Patient Global Itch Score**, and the **Dermatology Life Quality Index** (**23-28**).

V. Photographs of cutaneous lesions will be performed at baseline and at each follow-up visit for all enrolled patients.

Lesional (4mm) biopsies of a representative active area to be treated at study initiation and again at 8 weeks will be optional, but a goal of obtaining biopsies from ≥ 4 patients will be established. Biopsies will be evaluated for histologic features of DM by routine light microscopy. Additionally Nanostring PCR will be performed to assess for changes in RNA transcript levels and inflammatory cytokines related to DM and JAK-STAT pathways.

Research Procedures

I. Upon enrollment patients will undergo a thorough history (including assessing time of diagnosis), review of systems (including inquiry about photosensitivity), and a complete physical examination.

II. Patients will be prescribed 1.5% ruxolitinib cream to be used twice daily on affected areas (up to 20% BSA total) throughout the study period. All other previous/current topical medications will be required to be discontinued at least 2 weeks prior to this

point.

III. Patients will apply the first dose in clinic after all clinical assessments under the supervision of the PI to ensure they apply the correct amount to affected areas. Instructions to wait 8-12 hours between applications will be relayed. Patients will be provided with a drug diary to document number and times of applications on a day-to-day basis. If patients miss a dose, this should be documented but patients should not try to "make up" this dose by applying the medication more than twice on any given day. Adequate supplies of 1.5% ruxolitinib cream will be dispensed at each clinic visit during the study.

IV. Patients will be instructed to continue their current topical moisturizers, and sunscreen based on their current practice during the study period.

V. A detailed examination of the skin and mucous membranes will be performed, noting for presence/absence of the following: scalp erythema and atrophy, alopecia, heliotrope rash, typical erythema and atrophy of sun-exposed areas on the neck, upper chest and upper back (shawl sign), erythema +/- scaling of the elbows and/or knees (Gottron's sign), gottron's papules, periungual erythema, ragged cuticles, proximal nailfold capillary loops, palmar scaling and hyperkeratosis (mechanic's hands), a rash involving the hips (holster sign), oral ulcerations, cutaneous ulcerations, purpura.

VI. Objective cutaneous dermatomyositis scoring by the primary investigator using the **Cutaneous Dermatomyositis Disease Area and Severity Index** (CDASI) score **Physician Global Assessment** for (a) **skin activity** (b) **skin damage**, and **estimate of body surface area (BSA) involvement (handprint method)** with active dermatomyositis will be performed at each visit (**23-28**).

VII. Objective scoring tools to be completed by the patient at each visit will include: **Patient Global Skin Score** (0-10 visual analog scale), **Patient Global Itch Score** (0-10 visual analog scale), and the **Dermatology Life Quality Index** (validated quality of life assessment) (**23-28**).

VIII. Photographs of all cutaneous lesions will be performed at baseline and at each follow-up visit

IX. All patients will have a baseline **comprehensive myositis autoantibody panel** test

(Oklahoma Medical Research Foundation; https://omrf.org/research-faculty/core-facilities/myositis-testing/) to assess for presence of myositis-associated and myositis-specific autoantibodies.

X. Patients will be expected to continue their current systemic immunosuppressive treatment regimens throughout the study. If it is felt that patients should taper off of medications they will require a washout period **prior to starting the study**:

- corticosteroids- **4 weeks**
- methotrexate/azathioprine/mycophenolate/cyclosporine/tacrolimus/adrenocorticotropic hormone analogs/chlorambucil/cyclophosphamide/other systemic immunomodulatory agents- **4 weeks**
- Biologic medications (rituximab, etc.) and IVIG: - **5 half-lives or 12 weeks**.

XI. If it is felt that patients should start a new systemic medication they will require a period of **8 weeks** (60 days) on the medication prior to starting this study.

XII. Patients requiring live-attenuated vaccinations will need a 2 week "washout" period prior to enrolling in the study, and live-attenuated vaccines are not recommended during the treatment period.

XIII. Patients will require **follow-up visits in person at 4 weeks (+/- 5 days), 8 weeks (+/- 5 days) and 12 weeks (+/- 5 days)** after initiation of ruxolitinib 1.5% cream, at which time examinations and clinical scoring tool assessments will be repeated.

XIV. Ruxolitinib 1.5% cream will be discontinued in any given patient at the primary investigator's discretion if deemed necessary for the patient's overall health and well-being at any point during the study.

XV. To monitor safety and tolerability of 1.5% ruxolitinib cream, patients will be asked about any adverse symptoms at each clinic visit and instructed to call the investigators with any adverse symptoms that occur in between visits. Additionally, routine laboratory results (CBC and CMP) will be obtained and analyzed per routine intervals based on specific systemic medication regimens.

Primary end-point:

I. Improvement in **CDASI activity** by ≥ 25% (n=30) / 30% (n=20) / 35% (n=15) at **8 weeks**.
***primary end-point goal will depend on number of patients enrolled*

Secondary end-points:

I. Improvement in **CDASI activity** by ≥ 25% (n=30) / 30% (n=20) / 35% (n=15) at **12 weeks**.
***primary end-point goal will depend on number of patients enrolled*

II. Change in patient Global Itch Score by at least 2 points at 8 and 12 weeks.

III. Improvement in Physician's Global Assessment by at least 2 points at 8 and 12 weeks.

IV. Improvement in Global Patient Skin Score by at least 2 points at 8 and 12 weeks.

V. Improvement in the Dermatology Life Quality Index score by at least 2 points at 8 and 12 weeks.

VI. Improvement in % BSA of active DM rash by at least 1% at 8 and 12 weeks.

VII. Safety and tolerability of 1.5% ruxolitinib cream.

Exploratory end-points:

I. Changes in RNA transcript levels of inflammatory cytokines related to DM and JAK-STAT pathways at 8 weeks.

Study Assessments

Study Assessments	Baseline	4 weeks +/- 5d	8 weeks +/- 5d	12 weeks +/- 5d
Informed consent	**X**			
Medical history	**X**			
Physical Exam	X	X	X	X
CDASI	X	X	X	X
% BSA active skin disease (handprint method) (28)	X	X	X	X
PGA skin activity (VAS 10-point scale)	X	X	X	X
Patient Global Assessment Skin Activity Score (VAS 10-point scale)	X	X	X	X
Patient Global Itch Score (VAS 10-point scale)	X	X	X	X
DLQI	X	X	X	X
Photography	X	X	X	X
Skin Biopsy (subset of pts)	X		X	

Comprehensive Myositis Autoantibody Panel	X			
Pregnancy testing	X	X	X	X
IP application training	X			
IP administration in clinic	X			
Dispense IP	X	X	X	
Collect IP		X	X	X
Assess Compliance		X	X	X

Length of each test/procedure:

Modified CDASI: 5 min

% BSA: 5 min

PGA (VAS scoring): < 1 minute

Patient Global Skin Score (VAS scoring): < 1 min

Patient Global Itch Score (VAS scoring): < 1 min

DLQI: 5 min

****see references above associated with each individual test for details concerning validity and reliability**

Investigational Product materials and management

Information about drug
The IP is 1.5% ruxolitinib topical cream.

Packaging and dispensation of Investigational Product
The IP is a white-to-off-white cream containing 1.5% ruxolitinib and is supplied in 60g aluminum tubes. IP will be provided at each visit for a total of 3 months of IP application.

Storage and Handling of Investigational Product
The IP should be stored at 20°C to 25°C (68°F to 77°F), with excursions allowed from 15°C to 30°C (59°F to 86°F)

Application
The IP should be applied in a thin layer twice daily to affected areas of up to 20% body surface area. The Investigator will instruct the subject on how to apply the IP at the Baseline visit and the initial application of the IP will take place in clinic under observation. No other IP applications at subsequent visits will be required to be observed in the clinic setting.

In addition to the verbal instructions given during this visit, written instructions may be provided to the subjects. Subjects should apply twice daily applications of IP approximately 12 hours apart (between 8 and 12 hours). If an IP application has been missed or delayed such that there would be $<$ 6 hours between applications, the subject should not apply that dose of IP and just wait to apply the next dose. The importance of IP compliance should be discussed with the subject during each site visit.

Subjects will be instructed to store their IP in a secure location away from children. WOCBP should not come in contact with the IP unless using contraception as specified in this protocol.

If it is suspected that inappropriate amounts of IP are being applied by the subject further review of IP application in the clinic may be warranted.

Investigational Product Accountability and Disposal
Upon receipt of the IP, the Investigator (or designee, e.g., study center pharmacist) will acknowledge receipt of the IP after reviewing the shipment's content and condition. The Investigator (or designee) is responsible for ensuring that the designated study site staff conduct a complete inventory of study materials and assume responsibility for their storage and dispensing. The Investigator (or designee) must agree to keep all study materials in a secure location with restricted access. The Investigator (or designee) will keep a record of the inventory and dispensing of all IPs. This record will be made available to the Study Monitor for the purpose of accounting for all clinical supplies. Any significant discrepancy and/or deficiency must be recorded with an explanation.

All supplies sent to the investigators will be accounted for and, in no case, used in any unauthorized situation. Each tube of IP administered at the study center will be administered by qualified study center staff. At each site visit, IP compliance will be discussed with the subject.

At the end of the study, following final IP inventory reconciliation by the monitor, the study site will dispose of and/or destroy all supplies (including used, partially used, and/or unused tubes of IP) where possible, in compliance with the site's SOPs for IP disposal/destruction. In the event that the site is unable to dispose of and/or destroy IP supplies, the Sponsor will be notified and a third-party vendor may be contracted to manage destruction of IP supplies.

Data Analysis

Access to Data will be limited to the P.I., research coordinator, and research nurse. Approval from the IRB to allow access to data will be sought via an IRB amendment application if any additional research personnel are added to the study.

Confidentiality of patients will be protected by assigning numbers to patients and avoiding use of PHI. Results of the study will be reported in aggregate and anonymously

Statistical analyses will be conducted by the section of Biostatistics in the Quantitative Health Sciences department at the Cleveland Clinic using the methods described below:

Statistical Methods

Patient and disease characteristics will be summarized using means, standard deviations, medians and other percentiles of interest for continuous measures and frequencies and percentages for categorical factors. Changes in scoring tools and body surface area measures from baseline to 8 weeks will be calculated and compared using paired t-tests. If necessary, transformations of the data will be performed prior to analysis to meet distributional assumptions. If proper transformations cannot be found, then nonparametric Wilcoxon signed rank tests will be performed. To assess changes scores over time, linear mixed effect models will be fit and estimates of the average change per month will be calculated. Specific contrasts will also be created to estimate changes at 12 and 16 weeks relative to baseline and 8 weeks. Analysis will be performed using SAS software (The SAS Institute; Cary, NC). A significance level of 0.05 will be assumed for all tests. Correction for multiple testing is not planned, since the purpose of the present study is estimation.

Sample Size Considerations

The primary assessment tool will be the CDASI. Scores for the CDASI range from 0 to132 for the total score. In the paper by Yassaee (**29**), investigators found a mean (SD) total score of 20.10 (10.25). Given the apparent skewed distributions for this score, a log-normal distribution for the scores was assumed. Based on this estimate, a coefficient of variation (CV = Standard Deviation/Mean) of 0.6 appears appropriate.

Table 1 shows the minimum detectable decreases in CDASI scores, based on the assumptions above, and assuming use of two-sided paired t-tests on log-transformed values. These calculations further assume that a moderate positive correlation (r=0.5) between baseline and follow-up scores within person, and use of a 0.05 significance level. Under these assumptions, 15 patients are need to detect a 35% decrease in the mean CDASI activity score or CDASI total score with 80% power. Using the study by Yassaee as a reference, if the mean total score was 20, then there would be adequate power to detect decreases of 7 points in the mean total score. To detect smaller differences, the sample size increases rapidly. For example, to detect a 25% mean decrease (5 points) in CDASI score 29 patients would be required, while to see a 2 point mean difference (10% decrease), 203 patients would be needed.

These calculations do not incorporate drop out, so additional subjects may need to be enrolled if some patients fail to reach the 8 week follow-up period. Note that if variability is larger in the present study or correlation differs between group, the detectable differences may vary from the measures shown below.

Table 1. Minimum detectable differences are shown to detect specified differences in the mean CDASI scales at 8 weeks with 80% power and significance level of 0.05.

	Sample Size		
Scale	**10**	**15**	**20**
CDASI Total Score (CV = 0.6)	40%	35%	30%

<u>Adverse Events and Data Monitoring Committee (DMC)</u>

Patients will be instructed to call immediately with any adverse events during the administration of 1.5% ruxolitinib cream. The Principal Investigator (PI) must report all Serious

Adverse Events (SAEs) to Incyte within 24 hours of learning of an event, regardless of the PI's causality assessment. This notification should be provided on a completed Serious Adverse Event (SAE) form. SAE reporting for each subject begins the day the informed consent is signed by the patient and within 30 days after subject has completed or discontinued from the study or has taken last dose of the study drug, or as described in the protocol.

SAEs, occurring using Incyte study drug, are reported in accordance with the effective protocol. SAEs occurring with any other commercial drug are reported to the manufacturer of that drug in accordance with regulations and protocol.

Initial SAEs and/or subsequent follow-up reports should be reported via email to SafetyReporting@Incyte.com or fax (+) 1-866-981-2057. SAE reports should be for a single subject. SAE forms should be sent with a cover sheet and any additional attachments.

All adverse event information is reported to Incyte on the Principal Investigator's/Institution's Adverse Event Report Form, or a CIOMS-I or MedWatch Form FDA 3500A, or on an Adverse Event. Any serious adverse events will also be reported to the IRB in accordance with their policy.

- An interim analysis is not definitively planned, but will be considered for presentation purposes.

Consent

Consent will be obtained in a clinical setting at the baseline clinical appointment by a member of the study team at the time of planned enrollment. Vulnerable subjects will not be enrolled in this clinical study.

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