# Association of myalgias with compounded topical Janus kinase inhibitor use in vitiligo

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***Key words:*** creatinine phosphokinase; Janus kinase inhibitor; topical ruxolitinib; myalgias; vitiligo.

## INTRODUCTION

Current treatments for vitiligo include topical and systemic corticosteroids, topical calcineurin inhibitors, and phototherapy, but these treatments offer limited efficacy. Recent advances in understanding the immunopathogenic pathway in vitiligo suggest the potential utility of Janus kinase (JAK) inhibitors. Currently, oral ruxolitinib is approved by the US Food and Drug Administration (FDA) for use in polycythemia vera, myelofibrosis, and steroid-refractory graft-versus-host disease, and oral tofacitinib is FDA approved for use in rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. Neither of the topical formulations of these medications has FDA-approved indications; however, both the oral and topical forms have also shown promising results in their off-label use in dermatologic conditions such as vitiligo, alopecia areata/totalis, and atopic dermatitis.[1] Previously described adverse events for topical ruxolitinib include erythema, hyperpigmentation, and transient acne on applied sites with no severe or lasting side effects.[2] Here we present 2 patients with vitiligo who experienced myalgias after being treated with compounded topical ruxolitinib.

*Abbreviations used:*

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| CPK: | creatinine phosphokinase |
| FDA: | US Food and Drug Administration |
| JAK: | janus kinase |
| MKTP: | melanocyte keratinocyte transplant procedure |

## CASE PRESENTATIONS

The first case is of a 58-year-old Latina woman with a 4-year history of nonsegmental vitiligo with a total body surface area involvement of 2%. She was previously treated with pulse dexamethasone, 4 mg on Saturday/Sunday for 2 months, pimecrolimus cream, and home phototherapy. She underwent melanocyte keratinocyte transplant procedure (MKTP) in June 2019 to the right forehead, retroauricular area, posterior neck/upper back, left axilla, mons pubis, and labia majora. At the time of the MKTP procedure, the patient also had a few smaller vitiligo lesions on her posterior neck and was having depigmentation within scars on her right elbow and bilateral knees. Given the evidence of koebnerization, the patient was prescribed dexamethasone, 2 mg on Saturday/Sunday for 10 weeks. She was also directed to start applying compounded topical ruxolitinib 1.5% cream twice daily to any untreated vitiligo areas and then to apply the cream to treated areas 6 weeks after the MKTP. She started having severe myalgias in her left upper shoulder, left upper and lower extremities, and right lower extremities in September 2019. A creatinine phosphokinase level (CPK) was checked by her primary care physician in

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Funding sources: None.

Conflicts of interest: Dr Lyons is a subinvestigator for Incyte, Bayer, Unigen Inc, Lenicura, Estée Lauder, Miragen, Biofrontera, Pfizer, and L'Oréal. Dr Narla is a subinvestigator for Incyte, Lenicura, L'Oréal, Pfizer, and Biofrontera. Dr Hamzavi is an investigator for Unigen Inc, Allergan, Clinuvel, Galderma, L'Oréal, PCORI, Pfizer, Incyte Corporation, Bayer, Estée Lauder, Ferndale Healthcare Inc, Lenicura, General Electric, Janssen Biotech, and Johnson & Johnson. Dr Hamzavi is also the cochair of the Global Vitiligo Foundation (unpaid), is on AbbVie advisory board (unpaid), and is a consultant for Incyte. Dr Lim is an investigator for Incyte, Beiersdorf, L'Oréal, Pfizer, and PCORI; has served as consultant for Pierre Fabre, ISDIN, Ferndale, and Galderma; and has participated as a speaker in general educational session for Pierre Fabre, Eli Lilly, Johnson & Johnson, and Ra Medical System. Sandra Osaka has no relevant conflicts of interest to disclose.

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JAAD Case Reports 2020;6:637-9.
2352-5126



https://doi.org/10.1016/j.jdcr.2020.05.002

October 2019, which was elevated to 231 (reference range, 30-140 U/L) A repeat CPK a week later remained elevated (163) but was trending toward normal range, with normalization 2 months later in December. The patient had a remote history of back pain and unilateral ptosis. Her autoimmune/rheumatologic evaluation, done 2 years prior, showed positive antinuclear antibodies of 1:80 but negative dsDNA, SCL-70, SS-A, SS-B, RF, PM-SCL, Jo-1, and anti-Smith. C-reactive protein, erythrocyte sedimentation rate, thyroid, and complement levels were normal. She had no documented diagnosis of autoimmune/rheumatologic myopathy or neuromuscular disease prior to initiating JAK inhibitor therapy. She self-discontinued the topical ruxolitinib and had some improvement in the myalgias when seen at her dermatology visit in January 2020.

The second case is of a 44-year-old white man with a 5-year history of unstable acrofacial vitiligo with a total body surface area involvement of 4%. He was initiated on pulse dexamethasone, 4 mg on Saturday/Sunday, and compounded topical ruxolitinib 1.5% cream twice daily to the left hip. Soon after starting ruxolitinib, the patient had severe myalgias limited to the treatment area. CPK levels were not obtained. The patient had no history of arthritis, myopathy, or neuromuscular disorders. The patient self-discontinued the compounded topical ruxolitinib cream soon after starting and had complete resolution of symptoms. The patient stopped oral corticosteroids because of mood swings and insomnia soon after starting.

## DISCUSSION

Although treatment with oral JAK inhibitors has been associated with increases in CPK levels, myalgias, and arthralgias,[3] this side effect profile has not been reported for topical JAK inhibitor therapy.[4] In 2015, a study was performed to evaluate the results of 2 randomized controlled trials of oral JAK inhibitor therapy for chronic plaque psoriasis (OPT Pivotal 1 and OPT Pivotal 2). Across OPT Pivotal 1 and 2, 745 patients received tofacitinib, 5 mg; 741 received tofacitinib, 10 mg; and 373 received placebo. Of these patients, 20 of 745, 41 of 741, and 9 of 373 patients were observed to have increases in their CPK levels. Further, 5 treated patients and 2 placebo patients across the trials had their CPK level confirmed as more than 10 times the upper limit of normal.[5] Of these, 1 patient experienced mild-to-moderate myalgias, and 1 patient experienced mild arthralgias, both of which resolved. No other patients reported myalgia or other symptoms associated with CPK elevation. In patients with moderate-to-severe chronic plaque psoriasis treated with oral tofacitinib, although dose-dependent increase in CPK was recorded, no cases of rhabdomyolysis were reported.[5,6]

CPK is an enzyme that catalyzes the conversion of creatinine and adenosine triphosphate to phosphocreatine and adenosine diphosphate. Because this reaction is reversible, the phosphocreatine generated can be used to supply cells with their required adenosine triphosphate during high metabolic state. CPK is an intracellular enzyme located in tissues such as myocardium, skeletal muscles, and brain. However, with tissue injury, CPK is released into the bloodstream resulting in elevated serum levels.[7] In inflammatory conditions, inflammatory cytokines such as oncostatin M, may inhibit differentiation of myoblasts into mature myocytes. JAK inhibition may reverse this inhibition resulting in the differentiation of myoblasts to myocytes.[8,9] Although the exact mechanism of ruxolitinib-associated myalgias has not yet been fully elucidated, a potential explanation could be that the sudden increased myocyte differentiation and proliferation may cause muscle cell fragility and damage, thereby resulting in myalgias or myositis symptoms and increased serum CPK expression in a subset of patients treated with topical JAK-inhibitor.

The use of topical JAK inhibitors offers promise in the treatment of a variety of dermatologic conditions including alopecia, atopic dermatitis, psoriasis, and vitiligo.[4] In the cases presented here, it is important to note that the topical ruxolitinib was a compounded formulation; consequently, the results reported here may not extend to a noncompounded formulation. However, as these therapies gain popularity, it is important to be aware of potential adverse effects and publish more evidence on the safety and tolerability of these therapies.

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