Apremilast as a treatment for morphea: A case series

Merav Koschitzky, BA, and Saakshi Khattri, MD
New York, New York

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INTRODUCTION

Morphea, or localized scleroderma, is a skin condition characterized by erythematous and indurated inflammatory lesions that progress to atrophic and sclerotic plaques.[1] While the pathogenesis of morphea is complex, the fibrosis in morphea is believed to be immune-driven.[2] A recent study showing the anti-fibrotic effects of the phosphodiesterase 4 (PDE4) inhibitor apremilast in preclinical models of skin fibrosis suggested that patients with inflammation-driven fibrosis might respond to PDE4 inhibition.[3] Herein, we report improvement in treatment-resistant morphea in 5 patients treated with apremilast.

Abbreviations used:

IL: interleukin
PDE4: phosphodiesterase 4

Case 1

A 31-year-old woman presented for treatment of biopsy-proven morphea. Examination revealed hyperpigmented patches and plaques on the arms, legs, abdomen, back, and scalp. Some lesions had restricted skin mobility and dermal atrophy. Over the next 4 months, we treated the patient with calcipotriene, clobetasol, oral prednisone, and methotrexate (Table I); however, the lesions persisted (Fig 1, *A*). The patient developed elevated liver function tests while on methotrexate, which was subsequently discontinued. Off-label apremilast 30 mg twice daily was initiated after a starter pack. At the 4-month follow-up appointment, the patches appeared lighter, and the left forearm was no longer indurated (Fig 1, *B*). At 1-year follow-up, the hyperpigmented patches remained, but the skin was soft to the touch without atrophy. The left calf still had tight hyperpigmented patches. The next year, the patient returned for follow-up, complaining of increased tightness in the left forearm that started after she ran out of apremilast 1 month previously. Exam revealed irregular hyperpigmented patches throughout the body, mild skin thickening on the left forearm, and a new lesion on the flank that appeared shiny. Apremilast was restarted.

Case 2

A 30-year-old woman with a history of biopsy-proven morphea on her abdomen and back presented with a new lesion on her right flank (Fig 2, *A*). In the past, she had tried calcipotriene, mometasone, clobetasol, and intralesional triamcinolone injections; however, the lesions continued to increase in size and number, and the patient was reporting increased itching. Other treatment options were discussed, including phototherapy, methotrexate, and oral steroids. The patient deferred steroids due to concern about possible side effects, and deferred immunosuppressive agents including methotrexate due to the COVID-19 pandemic. Off-label apremilast was initiated, and other topicals were discontinued. At the follow-up visit 3 weeks later, the lesions were smaller, and no new lesions had appeared (Fig 2, *B*).

Case 3

A 29-year-old woman with history of morphea since childhood presented to our clinic upon noticing increased hyperpigmentation and a feeling of tightness in the lesions. Exam revealed hyperpigmented, slightly atrophic plaques on the right leg, right buttock, back of the right thigh, right forearm, back of the right shoulder, and the right side of the

From the Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York.
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Correspondence to: Merav Koschitzky, BA, Icahn School of Medicine at Mount Sinai, 5 E 98th St, New York, NY 10021. E-mail: Merav.koschitzky@icahn.mssm.edu.

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Table I. Clinical characteristics and treatments

Case	Therapies trialed prior to apremilast	*mLoSSI* before apremilast	*mLoSSI* after apremilast	*mLoSDI* before apremilast	*mLoSDI* after apremilast	Apremilast side effects
1	Calcipotriene* Clobetasol† Prednisone 60 mg daily for 1 week followed by a weekly dose reduction by 10 mg Methotrexate, 8 2.5-mg tablets once a week	5	1	4	1	None
2	Calcipotriene Intralesional triamcinolone 2.5 mg/mL × 0.5 mL Mometasone 0.1% ointment twice daily for several weeks Clobetasol	4	1	3	1	None
3	Calcipotriene Clobetasol Methotrexate 2.5-mg tablets, 8 tablets once a week for 8 months Cyclosporine 125 mg, once daily for 3 months	6	2	6	4	Nausea prior to dose reduction
4	Calcipotriene Betamethasone 0.05% ointment twice daily for several weeks Tacrolimus 0.1% ointment for several weeks Phototherapy 2-3 times/week at 3-4 minutes for 3 months Methotrexate, 5 2.5-mg tablets once a week for 3 months Tofacitinib 5 mg twice daily for 4 months (in combination with methotrexate)	7	2	3	1	None
5	Calcipotriene Triamcinolone 0.1% cream twice daily for 4 weeks	5	1	0	0	Nausea

mLoSSI, Modified Localized Scleroderma Skin Severity Index; *mLoSDI*, modified Localized Scleroderma Skin Damage Index.
*All calcipotriene was calcipotriene 0.005% ointment applied twice daily for at least 4 weeks.
†All clobetasol was clobetasol 0.05% ointment applied twice daily for at least 4 weeks.

lower abdomen with superficial dilated vessels and dermal and subcutaneous atrophy (Fig 3, *A*). The patient had used cyclosporine for 2 years upon initial presentation at the age of 13 but had not treated the morphea since. Over the next year, we treated the patient with calcipotriene, clobetasol, methotrexate, and finally cyclosporine with no adequate response. Off-label apremilast was initiated. At the 1-month follow-up, the abdominal lesion showed decreased vessel dilation, and the dermal atrophy (cliff-drop sign) had improved (Fig 3, *B*). The patient complained of nausea, which subsequently resolved after the dose was decreased to 30 mg once daily. Despite continued improvement over 2 months, the patient discontinued apremilast in preparation for a pregnancy, with plans to restart treatment afterwards.

Case 4

A 68-year-old woman presented for treatment of biopsy-proven morphea that was not improving with topical tacrolimus and betamethasone. Exam revealed erythematous slightly atrophic patches at the groin, on the abdomen, lateral aspect of the right breast extending toward the axilla, both forearms, and lower portion of the back. The forearms were indurated and showed dilated vessels, and the lower-back lesion showed impaired skin mobility. Over the next year, the patient trialed several therapies with inadequate improvement (Table I). No improvement was seen after topicals and phototherapy, and the lesions in the lower abdomen and inguinal area continued to progress.

The patient was then switched to methotrexate, and after 3 months, off-label tofacitinib was added due to inadequate response to methotrexate monotherapy. While on methotrexate and tofacitinib combination therapy, the erythema improved. However, new lesions appeared on the dorsal aspect of the hands and dorsal aspect of the left foot, and firmness and tightness of the skin persisted, especially over the lower back (Fig 4, *A*) and forearms. The patient also developed new-onset joint pain in the hands

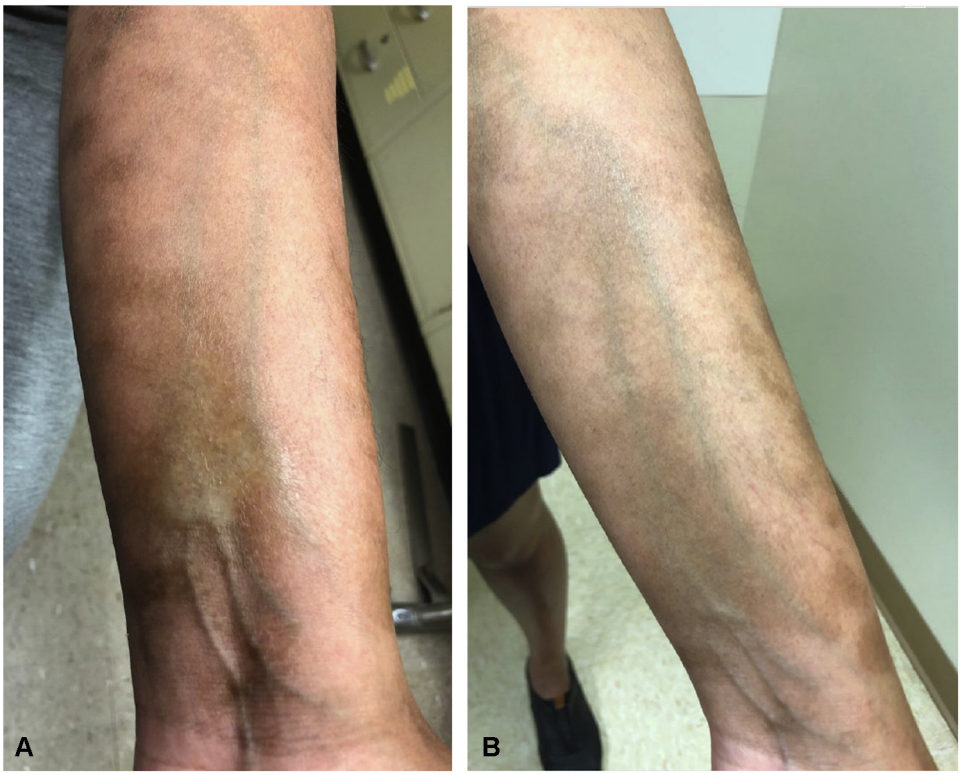

Fig 1. Morphea of left forearm before apremilast (**A**) and 4 months after apremilast (**B**).

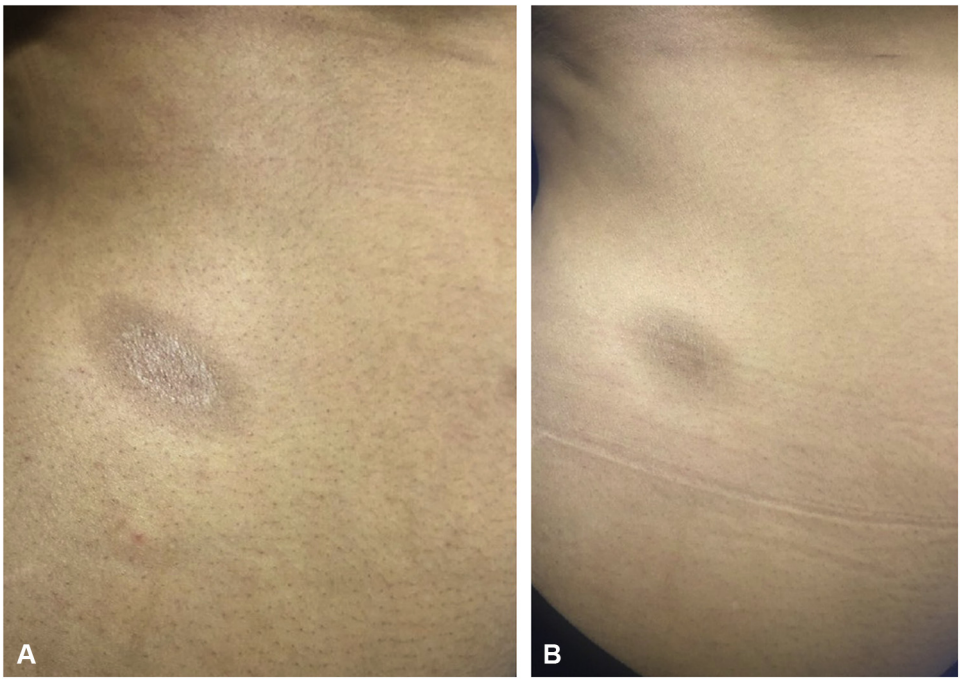

Fig 2. New morphea lesion on right flank before apremilast (**A**) and 3 weeks after apremilast (**B**).

and feet. Rheumatoid arthritis workup, including rheumatoid factor and anti-cyclic citrullinated peptide antibodies, was negative. Given her inadequate response after 4 months on tofacitinib and methotrexate, methotrexate was discontinued, and off-label apremilast was started in conjunction with tofacitinib. The patient reported improvement in erythema within 3 weeks. Further improvement

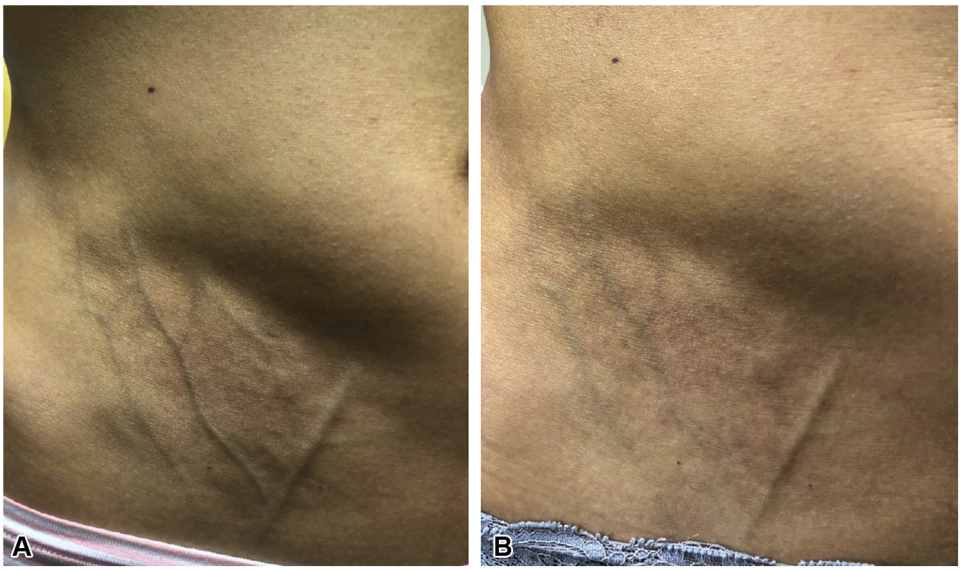

Fig 3. Morphea on abdomen before apremilast (**A**) and 1 month after apremilast (**B**).

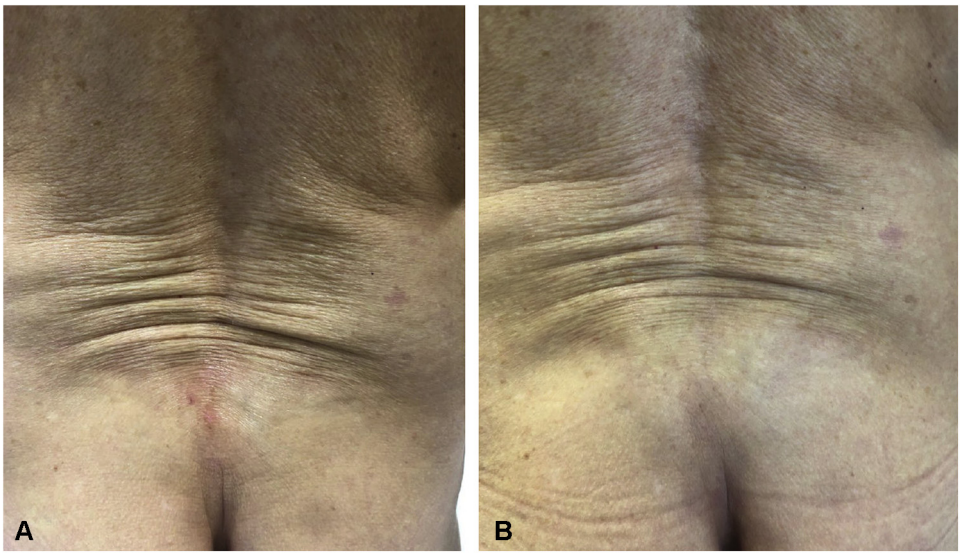

Fig 4. Morphea on the back before apremilast (**A**) and 4 months after apremilast (**B**).

was noted at 4-month follow-up, including resolution of the lower-back lesion (Fig 4, *B*) and increased mobility of her wrists and fingers. The patient remained on both apremilast and tofacitinib with no side effects.

Case 5

An 81-year-old woman presented to our clinic for treatment of biopsy-proven morphea that had failed to respond to calcipotriene and triamcinolone over the past year. Exam revealed erythematous patches and plaques on the bilateral antecubital fossa, forearms, wrists, abdomen, and bilateral hips extending toward the inguinal folds and suprapubic area (Fig 5, *A*). Risks and benefits of therapies were discussed. The patient deferred methotrexate due to possible side effects, including immunosuppression, and deferred phototherapy due to a family history of melanoma. The patient agreed to a trial of apremilast. One month later, there was some improvement in the erythema and size of the hip lesion (Fig 5, *B*), but other areas had not responded to the same degree. No new lesions had developed during this time. The patient complained of nausea, which persisted at the following month's visit despite a decrease in the dose from 30 mg twice daily to once daily. Due to nausea, apremilast was discontinued, and hydroxychloroquine was initiated.

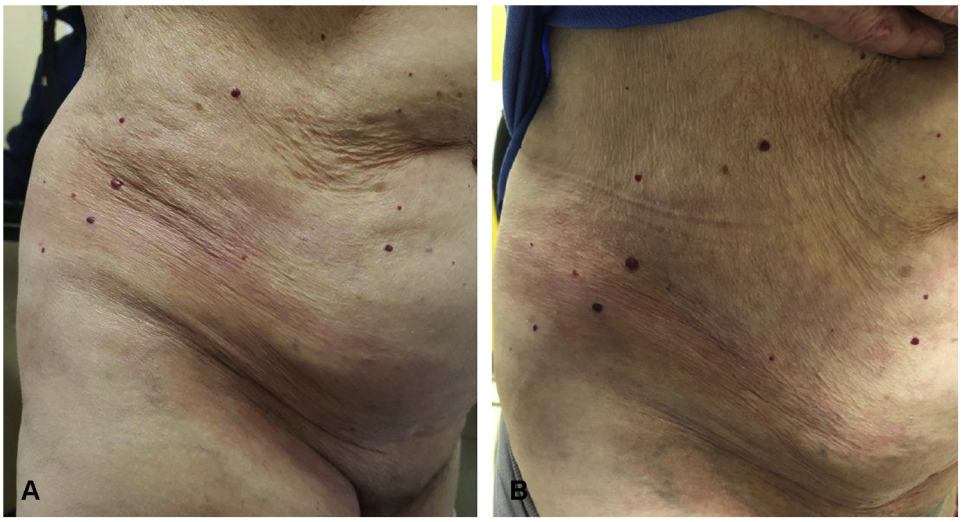

Fig 5. Morphea on right hip before apremilast (**A**) and 1 month after apremilast (**B**).

All patients received a starter pack of apremilast and then received 30 mg twice daily through insurance for off-label use.

DISCUSSION

Apremilast is an orally available small-molecule inhibitor of PDE4 that was approved for moderate-to-severe psoriasis and psoriatic arthritis in 2014. Apremilast's therapeutic action is likely related to the modulation of various inflammatory cytokines via increased cyclic adenosine monophosphate.[4]

The pathogenesis of morphea, while not completely understood, is partly related to immune dysregulation and inflammation via T helper 2 cell-related cytokines, including interleukin 4 and IL-6, that drive fibrosis.[2]

In a recent study, PDE4 blockade with apremilast had antifibrotic effects in animal models of skin fibrosis. By limiting M2 macrophage differentiation and IL-6 release, apremilast reversed fibrosis and prevented fibrosis progression. This study suggested that the inflammation-driven fibrosis in morphea might respond to PDE4 inhibition.[3]

Thus, we tried apremilast in 5 patients with biopsy-proven morphea and with inadequate responses or intolerable side effects to other treatments. Apremilast improved the appearance of morphea in our patients. Specifically, we saw reduction of erythema and lesion size, cessation of new lesion formation, softening of lesions, and decreased vessel dilation and dermal atrophy. One patient saw additional improvement in hand arthralgias, which are associated with morphea.[5] Positive results appeared to occur rapidly, with 4 patients reporting improvement in 1 month or less. At the time of manuscript preparation, 3 patients remained on apremilast. *Case 3* chose to temporarily discontinue treatment in preparation for pregnancy, and *case 5* discontinued treatment due to nausea.

Many treatments are used for morphea, including topical and intralesional corticosteroids, topical tacrolimus, calcipotriene, systemic immunosuppressants such as methotrexate, and phototherapy. However, little evidence exists to support the efficacy of these treatments for morphea.[6] Further, systemic immunosuppressants have serious adverse effects and require routine laboratory testing, and phototherapy is time-intensive, causing several of our patients to defer or discontinue these treatments. Apremilast does not require routine laboratory testing. A common side effect of apremilast is gastrointestinal upset that usually occurs within the first month and resolves over time.[7] In our study, 2 patients experienced nausea, which resolved in 1 patient with a smaller dose, and no patients reported diarrhea.

Overall, apremilast might be a useful alternative oral therapy for treatment-resistant morphea, or for patients with intolerance to the adverse effects of other immunosuppressants. Further studies are needed to assess the efficacy of apremilast for morphea.

Conflicts of interest

Saakshi Khattri is an employee of Mount Sinai and a consultant for AbbVie, Eli Lilly, Glenmark, Ichnos Sciences, Janssen, and Novartis. She serves on the Advisory Boards for Eli Lilly, Glenmark, Ichnos Sciences, Janssen, Novartis, and UCB. Merav Koschitzky has no relevant conflicts of interest to declare.

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