

Low-dose Methotrexate for Vitiligo

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ABSTRACT

Background: Treatment of vitiligo is aimed at repigmentation and often consists of multiple modalities, none of which are universally or rapidly successful. Extensive cases are most often treated with ultraviolet light therapy, which can be both costly and time-consuming. Though vitiligo is an autoimmune disease, there is no current data to support systemic immunosuppressive monotherapy.
Case Summary: Here we present a case series of 3 patients with vitiligo treated for 11-16 months with low-dose methotrexate (12.5-25 mg per week) with folic acid supplementation with clinically significant skin repigmentation, with response within 6 months in one case. There were no severe adverse effects reported.
Conclusion: These cases demonstrate an unexplored effective and steroid-sparing therapeutic alternative in patients with vitiligo for whom topical therapy has failed and phototherapy is cost-prohibitive or ineffective.

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INTRODUCTION

Vitiligo is an autoimmune leukodermic disorder of acquired skin depigmentation due to the destruction of melanocytes. Pigment loss can be stigmatizing and cause significant psychological stress, requiring early treatment with monitoring at regular intervals for improvement. Topical corticosteroids are usually first-line therapy followed by topical calcineurin inhibitors, particularly in cases with limited involvement. Narrowband ultraviolet B (NBUVB) radiation or other types of phototherapy are used in more extensive cases. Systemic corticosteroids are used rarely in rapidly progressive disease but cannot be used long-term due to well known side effects including weight gain and mood changes. Targeted immunotherapy is under development.[1] The use of other immunosuppressive or immunomodulatory agents is largely empiric, with limited data to support the use of azathioprine in combination with phototherapy.[2] Here we describe 3 cases of vitiligo with significant clinical improvement with low-dose methotrexate therapy.

Case Series

Case 1

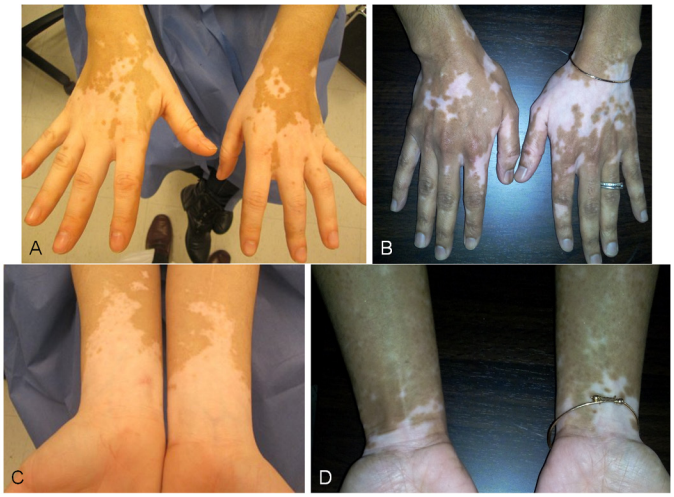
A 33-year-old otherwise healthy woman presented for dermatologic consultation with concern for rapidly progressive generalized vitiligo. Depigmentation was first noted in adolescence with significantly accelerated progression in the few months preceding presentation. At first presentation, she was initiated on a short course of prednisone due to rapid progression, with good response but lesion progression when taper was attempted. She then initiated ultraviolet B (UVB) radiation phototherapy three times per week in conjunction with topical 0.1% tacrolimus ointment. When there was no improvement after 6 weeks, she transitioned to narrowband UVB (NBUVB) phototherapy. With this treatment, she showed slow signs of perifollicular and patchy repigmentation with decreased body surface area (BSA) of disease for approximately 2 years. Throughout this time, she expressed concern for her ability to work given the time commitment needed for NBUVB therapy with moderate difficulty obtaining a home phototherapy unit. She then presented with concern for rapidly progressive flare while on treatment and expressed an interest in monobenzyl ether of hydroquinone depigmentation therapy.

On physical exam, the patient had Fitzpatrick skin type 4 with diffuse patches of depigmentation totaling more than 40% BSA, which was particularly troubling to the patient on the dorsal hands (Figure 1A and 1C). Given the patient's frustration with the long course of her disease and with concern for long-term steroid use, the decision was made to trial a systemic immunosuppressive agent. She was started on methotrexate 10 mg once a week with 1 mg folic acid supplementation daily and titrated up over 6 weeks to 17.5 mg methotrexate once a week. Extensive repigmentation was seen within 6 weeks of initiating treatment (Figure 1B and 1D). Of note, she experienced near resolution of digital involvement. Her liver function and blood cell counts are regularly monitored with no adverse side effects noted. She continues to improve to date with only 10% BSA remaining after 11 months of therapy and with no adverse events.

Case 2

A 46-year-old man with Fitzpatrick skin type 4 and an approximate 10-year history of vitiligo predominantly of the back and hands presented to a rheumatologist for treatment of psoriatic arthritis. He was initiated on methotrexate for his arthritis, titrated up to 25 mg per week with folic acid supplementation.

FIGURE 1. Repigmentation in vitiligo with low-dose methotrexate. Involvement of the dorsal (A) and ventral (C) hands and forearms prior to treatment and 6 months after treatment initiated (B and D).



After 7 weeks, he was noted to have improvement with thinner plaques and significantly improved joint pain. His vitiligo, previously unresponsive to 6 months of NBUVB phototherapy, was also noted to show clinical improvement when methotrexate was increased to 20 mg a week and above, after 14 months of therapy. No adverse effects were noted. The patient was lost to follow up after 16 months.

Case 3

A 26-year-old woman with Fitzpatrick skin type 3 presented to a rheumatologist with a 5-year history of rheumatoid arthritis (RA) initiated on methotrexate 7.5 mg a week 3 years previously. The patient self-discontinued methotrexate due to a concern for hair loss. She noted vitiligo that had been present since childhood but not active in recent years, that subsequently rapidly progressed to involve her face and trunk approximately 5 months after discontinuing methotrexate. She transitioned to sulfasalazine, hydroxychloroquine, and celecoxib for her RA, and then to etanercept, with a desire to avoid methotrexate in her childbearing years. She showed no improvement in skin pigmentation. Eight years later, etanercept was no longer sufficient for her RA. Methotrexate 7.5 mg a week with folic acid supplementation was added back on and increased to 12.5 mg a week. Remission of RA and significant skin repigmentation was noted 1 year after methotrexate initiation with no adverse effects.

DISCUSSION

Methotrexate is a folate anti-metabolite that competitively inhibits dihydrofolate reductase to inhibit DNA synthesis and repair. Originally developed as an antineoplastic agent, it has also been found to have anti-inflammatory and immunomodulating properties at low doses (5-25 mg weekly) and is FDA-approved for the treatment of psoriasis as well as RA. It has been shown by randomized controlled trial and systematic review to be effective in the treatment of RA.[3] While the mechanism of therapy is not fully understood, this suggests a role for methotrexate in the treatment of other immune-mediated dermatologic diseases such as vitiligo.[4]

Here we report significant repigmentation in 3 cases of vitiligo treated with low-dose methotrexate, one in which depigmentation was rapidly progressive and generalized. In two cases improvement was concurrent to the treatment of autoimmune arthritis. Improvement was noted as early as 6 weeks to 14 months, in two cases after the failure of a topical calcineurin inhibitor and phototherapy. Repigmentation appeared to be dose-dependent in at least one case. No serious adverse effects occurred in any of the 3 cases.

There is limited data evaluating the use of methotrexate as well as other systemic immunosuppressive therapies in vitiligo. Meta-analysis indicates that the literature regarding therapies for vitiligo is broadly limited by study size as well as combination treatment.[2] The cases presented here are notable for repigmentation after chronic, longstanding disease course, in one case with documented significant BSA involvement.

Methotrexate has comparatively low risk of side effects compared to other immunomodulatory agents, particularly at low doses and with folic acid supplementation[5]. It presents a promising alternative to long-term topical steroid use, systemic immunosuppression, or in cases in which phototherapy is not easily accessible. Larger scale studies evaluating short- and long-term efficacy of methotrexate therapy will significantly benefit the treatment of this common and psychologically debilitating disease.

DISCLOSURES

The authors have no conflicts of interest to declare.

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