

# Psoriatic flare after the concomitant administration of L-methylfolate and methotrexate



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## INTRODUCTION

Psoriasis is a chronic disease that causes erythematous patches with silver plaques and scales, often drastically affecting the quality of life of those afflicted by this disease. Psoriasis is a hyperproliferative disease, which is thought to be the result of a dysregulated immune system, specifically overactive T lymphocytes, which release excess proinflammatory cytokines and result in hyperproliferation of keratinocytes.<sup>1</sup> Treatment for psoriasis ranges from topical corticosteroids to systemic agents such as biologic immune suppressants. One such systemic agent, methotrexate, has been used to treat moderate to severe psoriasis for more than 40 years.<sup>2</sup> Methotrexate inhibits key steps in the metabolism of folic acid, a vitamin that contributes to numerous metabolic pathways necessary for cell survival.

Folate or folic acid is a B vitamin that is consumed in leafy greens or dietary supplements. These vitamins are necessary for crucial methylation reactions such as those seen in the synthesis of nitrogenous bases in DNA and RNA and to methylation reactions necessary for the production of amino acids and essential neurotransmitters. Metabolism of folic acid begins with its reduction into dihydrofolate and then tetrahydrofolate by dihydrofolate reductase (DHFR). Next, serine hydroxymethyltransferase converts tetrahydrofolate into 5,10 methylene tetrahydrofolate, which is converted to the metabolically active 5-methyl tetrahydrofolate (L-methylfolate) by methylenetetrahydrofolate reductase (MTHFR). Both the *DHFR* and the *MTHFR* genes are subject to numerous genetic differences that contribute to a variable rate of folate metabolism in the general population. Of note,

### Abbreviations used:

DHFR: dihydrofolate reductase  
MTHFR: methylenetetrahydrofolate reductase

methotrexate, which is used to treat cancers and autoimmune diseases including psoriasis, inhibits the DHFR enzyme, thereby preventing formation of active folate metabolites and inhibiting DNA replication and subsequent cell proliferation. In the case of psoriasis, methotrexate is thought to inhibit the growth of hyperproliferative T cells, preventing inflammatory damage to keratinocytes.

Because of its nonspecific mechanism of action, methotrexate often induces numerous peripheral adverse effects such as gastrointestinal discomfort and hepatic dysfunction. Folic acid is therefore administered concomitantly with methotrexate. Some studies, however, indicate that this combination may be associated with decreased efficacy of methotrexate.<sup>3-7</sup> L-methylfolate (Deplin Nestle Health Science; Pam Lab Inc, Covington, Louisiana) is a relatively new medical food used as an adjunctive therapy for treatment of depression. The mechanism of action is that L-methylfolate, the biologically active form of folate, is the only metabolite of folate that crosses the blood–brain barrier where it regulates the formation of the cofactor tetrahydrobiopterin (BH<sub>4</sub>), which is necessary for the synthesis of serotonin, dopamine, and norepinephrine. Because folate plays a crucial role in the central nervous system, it is proposed that individuals with decreased levels of it may experience higher rates of depression and experience a poor response

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to treatment with traditional antidepressants.<sup>8</sup> Administration of L-methylfolate, therefore, is thought to improve symptoms of depression by promoting central nervous system health, especially in individuals prone to poor folate metabolism. Because of the high bioavailability of this active folate metabolite in the peripheral system, it is plausible that administration of L-methylfolate would adversely interact with the mechanism of a folate antagonist such as methotrexate, perhaps to a higher degree than folate supplementation, although this has not been studied to date. Here we present the case of a patient successfully treated with methotrexate for chronic plaque psoriasis who experienced a sudden psoriatic flare after the use of L-methylfolate for the treatment of depression.

### CASE REPORT

A 53-year-old man presented to our practice in March 2016 with worsening symptoms of psoriasis despite continuation of methotrexate therapy. His medical history was significant for psoriasis, diagnosed at the age of 20, and major depressive disorder. Methotrexate, 30 mg weekly, and folic acid supplementation, 1 mg 6 times per week, were initiated 2 years earlier to treat psoriasis, which covered approximately 70% of his total body surface. This medication combination successfully treated the psoriasis for the last 2 years by resolving almost 100% of his psoriasis without significant gastrointestinal or other adverse effects. He noticed recurrence of prior psoriatic lesions and new psoriatic lesions covering 80% of his total body surface approximately 4 to 5 weeks after he began using L-methylfolate, 15 mg daily, for the treatment of depression. On examination, sharply demarcated, brick-red, scaly plaques were evident.

In addition to methotrexate and folic acid, the patient received a combination regimen of 0.005% calcipotriene cream, 0.05% desonide gel, 3 mg alprazolam for anxiety, 25 to 50 mg diphenhydramine for sleep, 60 mg duloxetine ER daily, and 300 mg bupropion daily for further treatment of depression. The patient reports being prescribed L-methylfolate by his psychiatrist for a recently discovered homozygous C677T mutation on the *MTHFR* gene, thereby decreasing his ability to reduce folate into the biologically active methyl-folate and possibly increasing his risk of poor response to psychiatric treatment. The patient reports transient improvement in depressive symptoms shortly after administration of L-methylfolate. Methotrexate was discontinued because of the worsening of his psoriasis symptoms, and he received his first dose of adalimumab, 0.8 mL subcutaneously, shortly after

discontinuation of methotrexate; he noticed improvements to his psoriatic lesions approximately 8 to 22 days thereafter. The patient reports experiencing a headache and nasal congestion immediately after administration of adalimumab but no other adverse effects. He remained stable at his most recent follow-up several months after administration of adalimumab.

### DISCUSSION

To our knowledge, this is the first report describing the interaction of L-methylfolate and methotrexate in the context of any medical condition. To date, treatment of psoriasis in patients receiving L-methylfolate specifically has not been studied and no guidelines have been established. The successful treatment by an immune biologic agent with an entirely different mechanism of action combined with the fact that this patient was stable on methotrexate before administration of L-methylfolate, suggests that a drug interaction between the 2 caused the patient's psoriatic flare. The medical literature reports that, consistent with our case, folate administered concurrently with methotrexate often alleviates side effects of methotrexate therapy but hinders efficacy of treatment.<sup>7</sup> Given that methotrexate's successful treatment of psoriasis is owing to inhibition of folate metabolism, it is logical that concurrent administration of L-methylfolate, folate's most biologically active metabolite, would significantly reduce its efficacy. Furthermore, the dose equivalence of folate and L-methylfolate is likely not equivalent, with L-methylfolate being a more potent chemical for many patients because conversion of folic acid to the biologically active L-methylfolate is highly variable owing to genetic variations and mutations in the *MTHFR* gene, resulting in many individuals who are unable to metabolize folate into L-methylfolate.<sup>9</sup> Therefore, L-methylfolate administered to a poor metabolizer of folate, such as the patient presented here, would result in a much higher equivalent dose than that of folate alone.

As a new and potentially more potent form of folic acid supplementation, L-methylfolate may cause significantly decreased methotrexate efficacy for the treatment of psoriasis, and providers should be aware of this possible drug interaction. In the future, dermatologists should consider the use of other systemic agents, such as the immunobiologics, to treat psoriasis in patients receiving L-methylfolate for depression. We present this case to highlight the implications of this new medication and how it may affect remission in psoriatic patients successfully treated with methotrexate.

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