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# Does daily folic acid supplementation reduce methotrexate efficacy?

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## Abstract

Methotrexate is a mainstay treatment for autoimmune and inflammatory conditions in the field of Dermatology. However, in some patients, its use is associated with significant side effects and toxicity. Folate supplementation with either folic acid or folinic acid often mitigates side effects and reduces the incidence of systemic toxicity related to methotrexate. Although the value of methotrexate is clear, debate remains about folate supplementation. There is little agreement about the proper dosing or frequency of folate supplementation as many believe that daily folate supplementation can reduce methotrexate efficacy. Although daily use of folic acid does not appear to affect methotrexate efficacy, dosing of folinic acid close to methotrexate administration may hinder methotrexate efficacy. Therefore, folic acid should be used daily with methotrexate to ameliorate side effects, whereas folinic acid should only be used for methotrexate toxicity.

*Keywords: methotrexate, folic acid, folinic acid, psoriasis, rheumatoid arthritis*

Methotrexate (MTX) is a folate antagonist that is an effective treatment for autoimmune and inflammatory conditions, but its daily use is limited by adverse effects (nausea, diarrhea, fatigue, mucosal ulceration). Although daily MTX dosing has potential for systemic toxicity (hepatotoxicity, bone-marrow suppression, pulmonary fibrosis, neurotoxicity), dosages of MTX for dermatologic conditions are relatively small and given only once weekly to produce less toxicity [1]. Whereas the

frequency of serious MTX toxicity is relatively low, mild adverse effects are seen in 5-35% of patients [2, 3]. Folate supplementation with either folic acid or folinic acid ameliorates side effects and reduces the incidence of hepatotoxicity, hematologic effects, and gastrointestinal intolerance without impairing MTX efficacy [4]. Additionally, patients receiving folate supplementation tolerate higher doses of MTX [5]. However, the most effective frequency of folate supplementation is not well characterized. Even though dermatology practitioners ranked third for generating the most MTX prescriptions, only 32% of dermatologists use folate supplementation in all patients on MTX [6].

The use of folic acid supplementation varies both in dosing and frequency. The optimal dosage of folic acid is still to be determined, with dosages varying from 1 to 5 mg/day to 5 or 35 mg/week [7]. Dermatologic usage is usually at the lowest end of that spectrum. There is also great variation in the regimen regarding folic acid supplementation. In a recent survey of dermatologists, 61% prescribed folic acid daily, 21% prescribed folic acid daily apart from the day of MTX administration, and 18% prescribed various other regimens. The regimen continues to be controversial because some physicians believe that folic acid on the same day as MTX may reduce MTX efficacy. Although 60% of dermatologists who prescribed folic acid believed that it did not reduce the efficacy of MTX in psoriasis, 33% were unsure, and 7% believed that folic acid did reduce efficacy [8].

The idea that daily folic acid decreases MTX efficacy may stem from previous reports regarding folinic acid. Continuous administration of folinic acid with

weekly oral MTX prevented improvement of psoriasis in patients. When folinic acid was stopped on the day of MTX, patients demonstrated improvement [9]. A study in rheumatoid arthritis patients found that a 15 mg weekly dose of folinic acid administered 2 hours after MTX reduced MTX efficacy, resulting in exacerbation of rheumatoid arthritis [10]. In another study, 15 mg of folinic acid was administered 4 to 6 hours after MTX administration. Although nausea was prevented, worsening of disease occurred in all patients [11]. Therefore, the timing of folinic acid supplementation may influence MTX efficacy. Studies in which folinic acid was given 24 hours after MTX administration showed no reduction of MTX efficacy [12].

Varying the dose and timing of folic acid does not appear to affect MTX efficacy, even at higher folate to MTX ratios [13, 14]. Furthermore, the bioavailability of MTX is unaffected by concomitant administration of 5 mg folic acid [15]. One explanation for the discrepancy may be competition between folinic acid and MTX for binding to cellular transport molecules during the distribution phase following MTX dosing, which does not occur with folic acid [12]. Given that folinic acid is more expensive, can affect MTX efficacy, and carries no advantage in prevention of MTX side-effects, there is no reason to use folinic acid in preference to folic acid for routine administration. However, folinic acid remains an important treatment for MTX overdose or acute hematologic toxicity.

Although there is almost unanimous agreement that efficacy is not hindered by folic acid supplementation in MTX-treated RA, there is conflicting research in MTX-treated psoriasis patients [4]. One study demonstrated that psoriasis patients on MTX supplemented with 35 mg/week of folic acid demonstrated no loss of efficacy [16]. Another study showed folic acid had no influence on MTX efficacy and some adverse effects of MTX recurred with the withdrawal of folic acid supplements [17]. Yet, two studies found outcomes contradicting previous reports. In the first study, folate supplementation had no significant improvement of adverse effects and antagonized MTX efficacy [18]. The second study demonstrated markedly different MTX efficacy in psoriasis patients on either MTX monotherapy or MTX with folic acid. This study concluded that MTX efficacy may be

significantly less if combined treatment with folic acid is used irrespective of high pre-treatment folate levels [19]. No definitive conclusions can currently be made when considering the findings of these last two studies.

Folate supplementation increases the chance of long-term, tolerable, and toxicity-free MTX treatment. Since beneficial effects of folic acid do not appear to depend on timing in most studies, it can be given daily, including the day of MTX administration. Folinic acid should only be used for MTX toxicity treatment because dosing folinic acid close to MTX administration may hinder efficacy.

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