

Low dose methotrexate

Going with the flow: methotrexate, adenosine, and blood flow

B N Cronstein

Methotrexate treatment modulates adenosine metabolism in patients with rheumatoid arthritis

Since its reintroduction for the treatment of rheumatoid arthritis (RA) in the 1980s,^{1,2} low dose methotrexate has become the favoured second line treatment for patients with RA and other forms of inflammatory arthritis. It is safe and effective; indeed, it is nearly as effective as the biological agents that seem to have transformed the treatment of RA, and the effects of biological agents combined with methotrexate are clearly better than either alone.³⁻⁷ Low dose methotrexate was introduced into the therapeutic armamentarium for RA on the basis of its ability to inhibit cellular proliferation, although the doses required for the antiproliferative effect in patients with cancer are considerably higher than those commonly used to treat RA (1–5 g in a bolus for cancer v 10–25 mg/week for RA). Thus, the mechanism by which methotrexate suppresses inflammation has been an area of some interest.

MECHANISMS OF ACTION

Several mechanisms of action have been proposed to explain the anti-inflammatory effects of methotrexate. Inhibition of purine and pyrimidine synthesis,⁸ suppression of transmethylation reactions and accumulation of polyamines leading to suppression of T cell function,⁹⁻¹¹ and promotion of adenosine release with adenosine mediated suppression of inflammation.¹²⁻¹⁵ The use of folic or folinic acid supplementation to prevent the toxicity of methotrexate without reversing its anti-inflammatory effects is not consistent with the notion that inhibition of purine/pyrimidine metabolism is responsible for the anti-inflammatory effects of the drug.^{8, 16-25} The absence of a suppressive effect on RA activity of an agent that directly inhibits transmethylation reactions renders this hypothesis untenable.^{15, 26} The third hypothesis, that methotrexate treatment increases adenosine release and adenosine mediates the anti-inflammatory effects of methotrexate still enjoys experimental support in in vitro and animal studies (recently reviewed¹⁵).

Strong evidence supporting the hypothesis that adenosine mediates the anti-inflammatory effects of methotrexate has been developed in patients as well. Thus, caffeine (contained in coffee), an adenosine receptor antagonist, appears partially to block the effects of methotrexate in patients with RA.^{27, 28} One of the earliest signs of a response to methotrexate in the synovium is diminished expression of the orphan receptor NURR1, a phenomenon shown to be mediated by methotrexate-induced adenosine release.²⁹ For technical reasons (adenosine has a half life in blood of about 2 seconds³⁰), it has been difficult to demonstrate that methotrexate treatment for inflammatory arthritis increases adenosine in blood or other bodily fluids, and the studies designed to test for changes in adenosine levels have been seriously flawed. In one study patients were given a dose of methotrexate and then immediately had blood and rectal fluid collected for measurement of adenosine,³¹ a design at odds with the long latent period required for the accumulation of the long lived methotrexate metabolites that mediate the adenosine release. Similarly, in another study patients were studied 1 week after receiving a single dose of methotrexate when, again, accumulation of long term metabolites and therapeutic response would not have been expected to have occurred.³²

EVIDENCE FOR THE EFFECT OF METHOTREXATE TREATMENT IN RA

Thus, in the paper by Riksen and colleagues published in this issue the authors provide some of the first evidence that methotrexate treatment for RA leads to altered adenosine kinetics in patients.³³ Adenosine, acting at its receptors in the vasculature, has long been known to be a potent vasodilator. Thus these authors examined forearm blood flow (FBF) responses to adenosine before and after 12 weeks of methotrexate treatment as a surrogate for methotrexate mediated alterations in adenosine metabolism. They found

that adenosine increased FBF much more in the patients after methotrexate treatment. Moreover, when they infused dipyridamole into the patients (which prevents adenosine uptake) they found a clear increase in FBF after methotrexate treatment. The authors noted that adenosine deaminase levels were significantly lower in lymphocytes after methotrexate treatment and suggested that this might account for the change in FBF responses. However, it is difficult to understand how a 25% decrease in adenosine deaminase activity in lymphocytes (but not erythrocytes) could significantly affect adenosine metabolism because most of the adenosine deaminase activity in blood is in the erythrocytes.

Another jarring note in this study is that although all the patients appeared to respond to methotrexate with altered adenosine kinetics, their arthritis did not respond to the drug, suggesting that either the joint tissue was unaffected or that methotrexate mediated alterations in adenosine levels may be necessary, but not sufficient, to suppress inflammatory arthritis. None the less, this work clearly demonstrates, using a surrogate marker, that methotrexate treatment modulates adenosine metabolism in patients with RA and provides further support for the hypothesis that increased extracellular adenosine mediates the anti-inflammatory effects of methotrexate.

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Correspondence to: Professor B N Cronstein, Department of Medicine, Pathology, and Pharmacology, NYU School of Medicine, 550 First Ave, New York, NY 10016, USA; Cronsb01@med.nyu.edu

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