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In juvenile idiopathic arthritis, is folate supplementation effective against methotrexate toxicity at the expense of methotrexate's efficacy?

Report by

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A 7 year old girl with sero-negative polyarticular juvenile idiopathic arthritis (JIA) has recently commenced weekly methotrexate (MTX). Within six months she develops painful aphthous ulcerations, alopecia, and generalised gastrointestinal upset. Her hepatic transaminases (AST/ALT) are now raised. Her parents are obviously distressed and have read on the internet about the role of folate supplementation in counteracting the adverse side effects of MTX. They have also read however, that this beneficial effect may be at the expense of the efficacy of MTX. They ask you, the prescribing physician, if this additional medication is warranted, and if so in what form?

Structured clinical question

In children with juvenile idiopathic arthritis [patient], does folate supplementation [intervention] counteract the adverse side effects and/or effect the efficacy of methotrexate [outcome]?

Search strategy and outcome

Secondary source: Cochrane Library, nil relevant.

Primary source: Medline via Pubmed: search terms "methotrexate" or "methotrexate efficacy" or "methotrexate toxicity", or "methotrexate side effects" and "juvenile arthritis" and "folinic acid supplementation" or "folate supplementation". Limits: all child: 0–18 years.

Search result: nine papers identified, three papers relevant. See table 3.

Search date: June 2005.

Commentary

Methotrexate, a dihydrofolate reductase (DHR) inhibitor, is now the leading disease modifying antirheumatic drug

(DMARD) used in the management of juvenile idiopathic arthritis. In a double blind, randomised controlled multicentre study, MTX was found to be efficacious in 63% (n = 127) of patients with resistant JIA, and it is now the standard first line agent in those with polyarticular disease.¹ Adverse reactions are generally mild and transient and it is generally well tolerated, much more so than in the adult population in whom approximately 30% will discontinue the drug one year after therapy is initiated.² Estimates for common toxicities range from 5% to 21%, with nausea (21%), vomiting (11%), mouth sores (10%), loss of appetite (7.5%), cited most commonly and hair loss (5%), malaise (5%), elevated liver function tests (5%), and leucopenia (5%) less commonly.³ Toxicity has been suggested to be a result of an induced state of folate depletion.⁴ The addition of folate has therefore been suggested to counteract the signs of toxicity, either as folic acid or the reduced form folinic acid which is able to function in biosynthetic pathways independent of DHR. Meta-analysis of seven trials assessing the benefits of folic and folate supplementation in rheumatoid arthritis (RA), clearly show a reduction in gastrointestinal and mucosal side effects.⁵ A randomised controlled study directly comparing folic acid to folinic acid in RA, showed no beneficial difference between the two forms of supplementation.⁶ Nevertheless, there is no consensus practise for folate supplementation in RA. The concern is that folate supplementation may have a detrimental effect on the therapeutic benefit of MTX. Folinic acid has been associated with a reduction in the effectiveness of MTX, thought to possibly be explained by competition between folinic acid and MTX for binding to cellular transport molecules.^{7–8} The same concerns exist for the paediatric population and where compliance is often an issue, any additional medication can be a great burden to the patient and family involved.

With the exception of a small case series (three patients) examining weekly folinic acid, neither folic acid or folinic acid have shown any reduction in the benefit of methotrexate administration in JIA.⁹ This effect however may have been as a result of a dosage effect. The folinic acid was administered at an equivalent dose to the methotrexate which is the dose required to reverse haematological toxicity.

In terms of reducing MTX toxicity, there may be evidence for weekly folinic acid at 25–50% of the MTX dose in diminishing hepatic and gastrointestinal related toxicities.¹⁰ The mean number of episodes per patient-year of hepatotoxicity and gastrointestinal toxicity decreased significantly after the start of folinic acid supplementation. Folinic acid was also reported to have a favourable response in the small case series above.⁹ As there was no reports of any MTX toxicity (hepatotoxicity measured only) in the study examining folic acid versus placebo, it is difficult to make any conclusion whether folic acid has any effect, beneficial or not.¹¹

The evidence for weekly folinic acid for diminishing MTX related toxicities is weak (grade 4) and limited. All three studies only address hepatic and gastrointestinal toxicity and no reference is made to other common toxicities such as mucositis. Despite the widespread and variable practise of prescribing folate supplementation to prevent or counteract MTX toxicity in JIA, to date there have been no trials comparing the efficacy of folic acid and folinic acid directly. No conclusions can be made regarding the effect of folate supplementation on methotrexate's efficacy in JIA.

The effectiveness, form, and dosage of folate supplementation for treating or preventing MTX related toxicities, and whether it has any effect detrimental or not on methotrexate's efficacy, needs therefore to be urgently determined in a prospective, randomised, double blinded, placebo controlled trial.

Table 3 Effect of folate supplementation on methotrexate toxicity and efficacy in JIA

Citation	Study group	Study type	Outcome	Key results	Comments
Ravelli <i>et al</i> (1999) ¹⁰	43 patients Ages 1.2–16 years Duration of JIA 0.5–8 years All previous toxic episode Folinic acid (25%–50%) MTX dose 24 hours after	Non-randomised retrospective case series (level 4)	Improvement of toxic episodes Episodes of disease flare Clinical remission	Hepatic and gastrointestinal toxicity episodes reduced Mean 2.30 (CI 95% –2.21 to 11.23) to mean 0.32 (CI 95% –0.76 to 2.02) Mean 1.09 (CI 95% –2.29 to 6.57) to mean 0.29 (CI 95% –0.62 to 1.76) Mean 0.30 (CI 95% –0.57 to 1.74) to mean 0.36 (CI 95% –0.84 to 2.25) p value ns Mean 0.17 (CI 95% –0.53 to 1.53) to mean 0.19 (CI 95% –0.65 to 1.39) p value ns	Small numbers No controls
Modesto <i>et al</i> (1996) ⁹	3 patients 2 SoJIA 1 Poly JIA Previous side effects Folinic acid (100%) MTX dose 4 hours after	Case series (level 4)	Resolution of side effects Disease flare	Gastrointestinal side effects Resolved in patients 1 and 2 Rash resolved patient 3 Flare of disease in all 3	Evidence very poor Folinic acid only
Hunt <i>et al</i> (1997) ¹¹	18 patients On MTX 6/12 or more Placebo versus 1 mg/kg/day folic acid	Randomised double blind crossover trial, 1 week washout (level 1b)	Disease flare (worsening of $\geq 2/5$ clinical variables) Hepatic toxicity (AST/ALT levels)	No significant change in either treatment group No abnormal ASDT/ALT	Figures for baseline Variables not given Study period very short.

CLINICAL BOTTOM LINE

- Methotrexate is generally well tolerated in children with juvenile idiopathic arthritis (JIA). (Grade B)
- Supplementing with folinic acid may counteract the most common side effects of methotrexate in JIA. (Grade C)
- There is insufficient evidence to conclude whether folate supplementation has any effect on disease modifying efficacy. (Grade D)

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