Cochrane for Clinicians

Putting Evidence into Practice

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Methotrexate Therapy for Rheumatoid Arthritis

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Clinical Question

Is methotrexate monotherapy appropriate for patients with rheumatoid arthritis, and do adverse effects of this treatment lead to discontinuation of therapy?

Evidence-Based Answer

Methotrexate monotherapy demonstrated statistically significant and clinically relevant improvement of symptoms and physical function compared with placebo at 12 to 52 weeks. Multiple adverse effects were reported with methotrexate use, and patients were twice as likely to discontinue methotrexate therapy when compared with placebo. (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

Rheumatoid arthritis is a chronic, inflammatory condition that can affect multiple joints, cause systemic manifestations, and lead to progressive disability as well as a decrease in life expectancy.[1] The American College of Rheumatology (ACR) recommends initiating treatment with disease-modifying antirheumatic drugs (DMARDs) as monotherapy or in combination with other nonbiologic (e.g., hydroxychloroquine [Plaquenil], leflunomide [Arava], methotrexate, minocycline [Minocin], sulfasalazine [Azulfidine]) or biologic (e.g., abatacept [Orencia], adalimumab [Humira], etanercept [Enbrel], infliximab [Remicade], rituximab [Rituxan]) DMARDs soon after diagnosis.[2] This is an update of a 1997 Cochrane review of the DMARD methotrexate.

The updated review includes 732 patients from seven trials comparing methotrexate monotherapy with placebo. The mean age of participants ranged from 46 to 60 years, and 74% were women. Weekly dosages of oral or parenteral methotrexate ranged from 5 to 25 mg, and follow-up ranged from 12 to 52 weeks. Patients in the methotrexate group were more likely to have 50% improvement in their symptoms at 52 weeks compared with the placebo group based on the ACR 50, which measures the number of tender or swollen joints and other outcomes such as pain and disability (relative risk [RR] = 3.0; 95% confidence interval [CI], 1.5 to 6.0; number needed to treat [NNT] = 7; 95% CI, 4 to 22). Statistically significant improvement in physical function was noted in patients receiving methotrexate (NNT = 4; 95% CI, 3 to 7). Radiographic scores did not improve, but the rate of radiographic progression was lower for patients in the methotrexate group (RR = 0.31; 95% CI, 0.11 to 0.86; NNT = 13; 95% CI, 10 to 60). The one study that measured remission did not find participants in either group who met the criteria for remission.

Adverse effects led to discontinuation in twice as many patients in the methotrexate group as the placebo group at 12 to 52 weeks (16% vs. 8%; RR = 2.1; 95% CI, 1.3 to 3.3; number needed to harm = 13; 95% CI, 6 to 44). The most common adverse effects were infections such as upper respiratory tract infection, bronchitis, and pneumonia. Rates of liver enzyme abnormalities, stomatitis and oral ulcers, alopecia, and gastrointestinal distress were also higher in the methotrexate group. Nine more persons out of 100 who took methotrexate vs. placebo withdrew from treatment because of adverse effects. On the other hand, there was no significant difference in total number of serious adverse effects between the methotrexate and placebo groups at 27 to 52 weeks.

The 2012 ACR guidelines recommend starting DMARDs such as methotrexate monotherapy for treatment of early (i.e., less than six months) and established (i.e., six months or more) rheumatoid arthritis in patients without poor prognostic features, and in combination therapy for early and established rheumatoid arthritis in patients with poor prognostic features.[2] Initial

treatment with methotrexate is also endorsed by the European League Against Rheumatism.[3] The American Board of Internal Medicine's Choosing Wisely initiative, in collaboration with the ACR, recommends a three-month trial of methotrexate or other conventional nonbiologic DMARDs before prescribing biologic DMARDs.[4]

SOURCE: Lopez-Olivo MA, Siddhanamatha HR, Shea B, Tugwell P, Wells GA, Suarez-Almazor ME. Methotrexate for treating rheumatoid arthritis. *Cochrane Database Syst Rev.* 2014;(6):CD000957.

The practice recommendations in this activity are available at http://summaries.cochrane.org/CD000957.

Author disclosure: No relevant financial affiliations.

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3. Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis.* 2014;73(3):492-509.
4. American College of Rheumatology. Focus on patient care: Choosing Wisely. http://www.rheumatology.org/FiveThings/. Accessed September 7, 2014.

Zinc Supplementation in Children Six Months to 12 Years of Age

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Clinical Question

Does zinc supplementation prevent mortality, morbidity, or growth failure in children six months to 12 years of age?

Evidence-Based Answer

Preventive zinc supplementation for children in low- and middle-income countries appears to reduce rates of diarrhea and may slightly reduce rates of growth failure. (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

Pneumonia and diarrhea cause approximately 15% and 10%, respectively, of deaths in children younger than five years around the world, and malaria accounts for 15% of deaths in this age group in sub-Saharan Africa.[1] Because approximately 17% of the world's population is at risk of inadequate zinc intake, and because the prevalence of inadequate zinc intake is correlated with the prevalence of growth stunting,[2] zinc supplementation has been proposed as a way to address targeted child health outcomes including infectious diseases, growth, and mortality in areas where diets are deficient in zinc. However, to date there are no standardized recommendations for dosing or duration of preventive zinc supplementation.

This Cochrane review incorporates data from 80 randomized controlled trials with a total of 205,923 participants specifically evaluating the use of zinc as a supplement for preventing death from diarrhea, lower respiratory tract infection, or malaria, as well as for reducing rates of all-cause mortality and growth failure. The authors did not include studies of food fortification with zinc or use of zinc as a therapeutic intervention. Seventy-three studies (91%) were from low- or middle-income countries, and seven (9%) were from North America or Europe. The included studies used a wide variety of zinc formulations, and the duration of preventive supplementation ranged from less than two months to 11 months or more.

Childhood mortality is not affected by zinc supplementation. The 13 included studies that addressed all-cause mortality did not find a statistically significant effect of zinc supplementation (relative risk [RR] = 0.95; 95% confidence interval [CI], 0.86 to 1.05), and there was no evidence from included studies that zinc supplementation reduced disease-specific mortality caused by diarrhea (RR = 0.95; 95% CI, 0.69 to 1.31), lower respiratory tract infection (RR = 0.86; 95% CI, 0.64 to 1.15), or malaria (RR = 0.90; 95% CI, 0.77 to 1.06).

The impact of preventive zinc supplementation on serious childhood infections is more ambiguous. Studies in the review demonstrated reductions in the incidence (RR = 0.87; 95% CI, 0.85 to 0.89) and prevalence (RR = 0.88; 95% CI, 0.86 to 0.90) of all-cause diarrhea, but there was no evidence of reductions in the incidence (RR = 1.05;

95% CI, 0.95 to 1.15) or prevalence (RR = 0.88; 95% CI, 0.47 to 1.64) of malaria. The studies also showed a possible increase in the prevalence of lower respiratory tract infection (RR = 1.20; 95% CI, 1.10 to 1.30).

There appears to be some benefit of zinc supplementation on growth-related outcomes. The included studies demonstrated small but statistically significant beneficial effects of zinc on height (standardized mean difference [SMD] = −0.09; 95% CI, −0.13 to −0.06), weight (SMD = −0.10; 95% CI, −0.14 to −0.07), and weight-to-height ratio (SMD = −0.05; 95% CI, −0.10 to −0.01), although zinc supplementation does not appear to reduce the prevalence of stunting.

Although the authors of this Cochrane review did not find a statistically significant reduction in all-cause or disease-specific mortality from preventive zinc supplementation, reductions in the risk of diarrhea and improvements in growth measures are encouraging. Childhood mortality is multifactorial, especially in low- and middle-income countries. Preventive zinc supplementation is not a panacea. However, particularly for physicians in public health or policy-making roles, zinc supplementation does appear to be at least one potentially beneficial piece of the puzzle for reducing rates of diarrhea and growth restriction among children with zinc-deficient diets.

SOURCE: Mayo-Wilson E, Junior JA, Imdad A, et al. Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age. *Cochrane Database Syst Rev.* 2014;(5):CD009384.

The practice recommendations in this activity are available at http://summaries.cochrane.org/CD009384.

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