ONE MINUTE CONSULT

BRIEF QUESTIONS AND ANSWERS ON CURRENT CLINICAL CONTROVERSIES

Q: Should methotrexate be a first-line treatment for rheumatoid arthritis?

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Lingering doubts about methotrexate have been answered

A: NOT ONLY MUST an agent used to treat rheumatoid arthritis be beneficial in the short term, it must both be relatively safe and maintain its effectiveness over the long term. Because methotrexate has a rapid onset of action (3–6 weeks) and works better than most other drugs, some experts felt, as early as the mid-1980s, that it should be considered as a first-line disease-modifying drug for rheumatoid arthritis.[1] However, in an essay published in 1990, Furst[2] argued that methotrexate should not be the first disease-modifying drug chosen because many questions remained to be answered, among them:

- Was methotrexate capable of slowing radiographic progression?
- What was the true frequency and impact of long-term liver toxicity?
- How did methotrexate compare with other disease-modifying agents?
- What drug reactions might occur when methotrexate was combined with other agents?

Since that time, these questions have been addressed and answered.

Methotrexate is effective

Radiographic studies indicate that methotrexate reduces the frequency of erosions and increases the frequency of healing more effectively than other disease-modifying drugs,[3,4] although it does not halt the progression of rheumatoid arthritis.

In addition, its early use may lead to clinical remission. A preliminary, observational, retrospective cohort study[5] demonstrated a higher frequency of remission in 28 patients initially given methotrexate than in 55 matched controls treated initially with other disease-modifying drugs.

Methotrexate is safe

Recent meta-analyses and comparative studies have demonstrated that methotrexate is not only the most effective but also among the safest of existing disease-modifying drugs for rheumatoid arthritis.[6–9] For example, in one series,[9] 60% of patients continued to take methotrexate for 5 years vs fewer than 25% for all other disease-modifying drugs.

The risk of long-term liver toxicity appears to be low, with cirrhosis occurring in approximately 1 of 1,000 patients treated for 5 years.[10] This frequency is so low that routine liver biopsy is no longer recommended.[11]

Recent reviews have also shown the relative safety and added benefit of methotrexate when it is combined with other disease-modifying drugs.[12,13] The list of drugs that can be combined with methotrexate continues to grow and now includes anti-tumor necrosis factor-alpha[14] and leflunomide.[15]

Precautions

The long-term safety of methotrexate depends on selecting appropriate patients. Do not give methotrexate to patients who:

- Have renal or hepatic impairment
- Use alcoholic beverages regularly
- Have primary hematologic diseases
- Are taking trimethoprim-sulfamethoxazole long-term

Prescribe folic acid 1 mg/day for all patients receiving methotrexate.[16]

Monitor patients for potential adverse effects on a regular basis. In particular, obtain a:

- Complete blood count
- Serum creatinine level
- Aspartate aminotransferase (AST) level (formerly known as serum glutamic oxaloacetic transaminase—SGOT)
- Serum albumin level (perhaps).

Conclusion

Methotrexate should be used as a first-line disease-modifying drug for patients with moderately active rheumatoid arthritis (defined as elevated acute-phase reactants and five or more swollen joints).[12]

REFERENCES

1. **Wilke WS, Mackenzie AH.** Methotrexate therapy in rheumatoid arthritis. Current status. Drugs 1986; 32:103–113.
2. **Furst DE.** Proposition: methotrexate should not be the first second-line agent to be used in rheumatoid arthritis if NSAIDs fail. Semin Arthritis Rheum 1990; 20:69–75.
3. **Alarcon GS, Lopez-Mendez A, Walter J, et al.** Radiographic evidence for disease progression in methotrexate treated and non-methotrexate disease modifying antirheumatic drug treated rheumatoid arthritis patients: a meta-analysis. J Rheumatol 1992; 19:1868–1873.
4. **Drosos AA, Tsifetaki N, Tsiakoue K, et al.** Influence of methotrexate on radiographic progression in rheumatoid arthritis: a 60-month prospective study. Clin Exp Rheumatol 1997; 15:263–267.
5. **Bologna C, Jorgensen C, Sany J.** Methotrexate as the initial second-line disease modifying agent in the treatment of rheumatoid arthritis patients. Clin Exp Rheumatol 1997; 15:597–607.
6. **Felson DT, Anderson JJ, Meenam RF.** Use of short-term efficacy/toxicity trade-offs to select second-line drugs in rheumatoid arthritis: a meta-analysis of published clinical trials. Arthritis Rheum 1992; 35:1117–1125.
7. **Fries JF, Williams CA, Ramey D, Bloch DA.** The relative toxicity of disease-modifying antirheumatic drugs. Arthritis Rheum 1993; 36:297–306.
8. **Wolfe F, Hawley DJ, Kathey MA.** Termination of slow-acting anti-rheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol 1990; 17:994–1002.
9. **Pincus TE, Marcum SV, Callahan LF.** Long-term drug therapy for rheumatoid arthritis in 7 rheumatology private practices: 2. Second-line drugs and prednisone. J Rheumatol 1992; 19:1885–1894.
10. **Kremer JM, Lee RG, Tolman KG.** Liver histology in rheumatoid arthritis patients receiving long-term methotrexate therapy: a prospective study of baseline and sequential biopsy samples. Arthritis Rheum 1989; 332:121–127.
11. **American College of Rheumatology Ad Hoc Committee on Clinical Guidelines.** Guidelines for monitoring drug therapy in rheumatoid arthritis. Arthritis Rheum 1996; 39:723–731.
12. **Wilke WS, Cash JM.** The use of slow-acting (Class III) symptom-modifying anti-rheumatic drugs in rheumatoid arthritis. Clin Immunother 1996; 5:309–325.
13. **O'Dell JR.** Methotrexate use in rheumatoid arthritis. Rheum Dis Clin North Am 1997; 23(4):779–796.
14. **Maini RN, Breeddeld FC, Kalden JR, et al.** Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998; 41:1552–1563.
15. **Weinblatt ME, Kremer JM, Coblyn JS, et al.** Leflunomide plus methotrexate in refractory rheumatoid arthritis: a pilot study [abstract]. Arthritis Rheum 1997; 40(suppl):S193.
16. **Morgan S, Baggott JE, Vaughn WH, et al.** Supplementation with folic acid during methotrexate therapy for rheumatoid arthritis. Double-blind, placebo-controlled trial. Ann Intern Med 1994; 121:833–841.

Q: Should all diabetic patients take ACE inhibitors, even those without proteinuria?

ACE inhibitors are not yet recommended for all diabetic patients

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A: RECENT STUDIES have shown that angiotensin-converting enzyme (ACE) inhibitors can slow the progression to diabetic nephropathy in patients with type 1 or type 2 diabetes with microalbuminuria or macroalbuminuria.

Should we extend this reasoning, and give all patients with diabetes ACE inhibitors, even if they have no proteinuria?

I believe it is premature to recommend using ACE inhibitors in *all* patients with diabetes mellitus. We do, however, have good evidence that ACE inhibitors are beneficial in *specific* groups of diabetic patients, eg, those with microalbuminuria or frank proteinuria. There is also accumulating evidence of benefit in patients with congestive heart failure and myocardial infarction. Whether these indications should be expanded awaits the results of further study.

Blood pressure and the kidney

A major principle to protect the kidney from the complications of diabetes is to treat high blood pressure aggressively, no matter what type of antihypertensive drug is used. In early studies in patients with type 1 diabetes, Parving et al[1] and Mogensen[2] used antihypertensive drugs such as diuretics, beta-blockers, and hydralazine; they demonstrated that lowering blood pressure reduces proteinuria and slows the decline of renal function.

Current guidelines suggest that a value less than 130/85 mm Hg is a reasonable target. Whether lower blood pressures will accrue greater benefits is not yet firmly established.

ACE inhibitors and renal disease in diabetes

Although the primary goal in protecting the kidney is to reduce the blood pressure, a preponderance of current evidence indicates that ACE inhibitors protect the kidney better than other blood-pressure-lowering medications,