Methotrexate and emerging therapies

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ABSTRACT
More publications in the medical literature have described the clinical efficacy and toxicity of methotrexate (MTX) than of any other drug ever used for rheumatic diseases. A knowledgeable clinican can thus rely on evidence-based medicine to guide the use of this agent. Because MTX is not remission-inducing, many new therapies are being combined with it in order to achieve a greater therapeutic response. This trend will likely continue and expand as more novel agents are introduced.

Introduction

It is only within the past decade that methotrexate (MTX) has become the dominant second-line agent to treat patients with rheumatoid arthritis (RA). An unprecedented number of clinical studies have shown that MTX is effective when other second-line agents have failed (1-3) and is generally well tolerated over long periods (3-9).

MTX is not an ideal therapeutic agent because its use is associated with serious potential toxicity. What is different about MTX is that so many of the complex management issues associated with the use of this agent that can do so much, good and bad, have been studied. An informed and experienced clinician can therefore use the drug with skill and rely on evidence-based medicine to avoid many problems. Indeed, it can be objectively stated that there has never been so much written about any single agent used in the treatment of patients with rheumatic disease as has been written about MTX.

Liver toxicity and liver biopsies can be avoided if patients forego alcohol and clinicians adjust the weekly dose of the drug to avoid elevation in transaminase enzymes or a decrease in serum albumin (10, 11). While other MTX toxicities, especially lung toxicity, remain worrisome, the recent identification of risk factors for the pulmonary reaction that may occur with MTX (12), and the clinical description of the syndrome (13) should make avoidance and recognition somewhat easier.

We have learned a great deal more about the molecular nature of mediators of the disease process we call RA than we knew when MTX first gained popularity over a decade ago. Researchers have described in exquisite and remarkable detail the structure and function of the major histocompatibility complex (MHC) and the T cell receptor, and the sequence of molecular signaling events which are necessary for their interaction. Cellular adhesion molecules, cytokines, growth factors, chemokines, and their naturally occurring inhibitors govern the healthy and diseased states (14). The new knowledge of the interplay of these mediators has given rise to the emergence of strategies to interfere with a specific step that may be associated with a worsening of clinical symptoms, because it has become possible to provide the RA patient with another naturally occurring molecular species in order to lessen inflammation. We are witness to a variety of strategies which logically seek to inhibit cytokines like tumor necrosis factor α (TNFα) or interleukin (IL)-1β, which are known to contribute to the inflammatory response, while others are testing IL-10 or IL-4 which shift the molecular balance away from these disease mediators.

A new role for MTX

How do these new strategies relate to MTX and what clinical practice patterns are we likely to see emerge? It is of course impossible to predict the future with certainty, but the events of the last several years might allow some reasonable prognostications. Many agents are and will be combined to derive the maximum therapeutic effect.

A general consensus has emerged that most patients with moderate or severe RA should be treated aggressively to best avoid the bony destruction, deformity, and disability that so often accompany the disease. Although MTX may be the most effective single agent now available, it does not induce remissions in

most patients. Furthermore, some patients require higher doses of MTX with time in order to maintain efficacy (6), while others are unable to tolerate a high enough weekly dose to achieve the desired response. New combinations of existing drugs added to MTX have been shown to provide additional benefit over treatment with MTX monotherapy (13, 15, 16).

The biological therapies now being developed are therefore being used in combination with MTX. The therapeutic goal which is described with increased frequency is no less than remission of disease. While this may seem overly ambitious to some, it is clear that many patients will do better, at least in the short-term, when these agents are combined with MTX.

The number of potential combinations is quite large. Studies of combinations of newly released agents can and will be performed by curious and industrious researchers in a Rheumatoid Arthritis Investigational Network (RAIN)-type model network (15). The outcome of these hypothetical investigations remains years away. In the mean time, we must await the results of ongoing trials of one new agent at a time used with MTX.

The new role for MTX will be that of a centerpiece used to support other therapeutic interventions. At present, these combinations are somewhat arbitrary and are driven by the economics of drug development rather than a clear, scientific rationale. Because MTX does so many different things within a cell, it is not exceedingly difficult to develop a strategy to combine almost any category of drug with it. Of course, ideal combinations would have a complementary mechanism of action without additive toxicity. Presently, the toxicities of MTX are much better defined than its mechanism of action (17, 18).

The very uncertainty about the precise mechanism of action of MTX in human beings with RA provides a therapeutic opportunity for combining the drug with almost any agent, as long as serious additional toxicity can be avoided. Studies of the potential pharmacokinetic interactions of MTX with other agents will be needed in order to determine whether an observed benefit or additional toxicity could be due to alterations in the metabolism of MTX or inhibition of renal excretion. Agents with potential hepatotoxicity must be carefully monitored when combined with MTX. It is likely that some liver biopsies will be needed when an agent with potential hepatotoxicity is combined with MTX.

Because of possible additive immunosuppression, with its potential for malignant transformation or opportunistic infection, careful monitoring of new agents used in combination with MTX in long-term studies will be required. MTX is associated with the development of lymphoma (19), which has been difficult to separate from the increased incidence of non-Hodgkin's B cell lymphoma seen in patients with RA (20). Several of the combination strategies now being employed with MTX, including some synthetic oral agents as well as cytokine or T cell inhibition, have the potential to increase the risk for these adverse outcomes, and it is only with the passage of years that we will be able to judge whether these problems emerge. These issues are summarized in Table I.

New interventions versus MTX

As already stated, MTX does not induce remission in most patients, and its use is associated with the potential for serious toxicity. It is possible that one or more of the new interventions that are now being studied in clinical trials will be found to be as effective as, or even more effective than MTX, but without MTX's potential for serious toxicity. Investigations comparing efficacy will be meticulously performed with randomization of equivalent disease duration, joint damage, and activity between study groups. The treatment duration should be at least one year, as earlier well-conducted studies failed to show a difference between MTX and auranofin over 6 months (21), whereas a difference was observed over 9 months (8).

Several possible scenarios could be imagined, depending upon the outcome of trials of MTX versus these new agents. For the purposes of comparison in this discussion, it will be assumed that any of these novel agents will have already achieved Food and Drug Administration approval and be prescribed as single drug therapy.

Scenario one is the use of an intervention which is not as effective as MTX, but which results in statistically significant and clinically meaningful responses from baseline. It would be difficult to

Table I. Potential risk of combining new agents with MTX to treat patients with severe rheumatoid arthritis (RA).*

Agent	Possible interaction with MTX	Demonstrated	Theoretical
Cyclosporine	Decreased glomerular filtration rate, with impaired renal excretion of MTX	30% increase in MTX AUC when drugs are combined	
Sulfasalazine	Additive folate inhibition results in increased toxicity	No	+
Leflunomide	Additive hepatic or marrow toxicity	No	+
Mycophenolate, Mofetil	Additive hepatic or marrow toxicity	No	+
TNFα inhibition	Opportunistic infection, malignancy	No	+
IL-1 receptor antagonist	Opportunistic infection, malignancy	No	+

* For the purpose of the table we will assume the additive benefit.
MTX: methotrexate; AUC = Area under the serum concentration curve; TNFα: tumor necrosis factor α; IL-1: interleukin-1.

Table II. Factors influencing the choice of a therapeutic agent for patients with rheumatoid arthritis (RA) when the agent's effectiveness equals that of methotrexate (MTX).

For MTX use	Against MTX use
Best-studied long-term agent used in RA	Pre-existing hepatic, renal, or pulmonary disease
Toxicity manageable based upon peer-reviewed journal articles	Patient who does not wish to discontinue alcohol
Documentation of long-term tolerability	Recent history of malignancies
Widespread physician acceptance	Pre-existing population which has failed or not tolerated it
Can be taken orally (only relevant for biotech interventions)	
Expense	
Fear of unforeseen safety issues with new drug	

(Assumes agents would be used as single-drug therapy.)

develop a compelling reason to use the new intervention alone under these conditions except under the following circumstances: (1) an individual has failed or is unable to tolerate MTX; (2) an individual does not wish to forego social alcohol consumption; (3) underlying lung disease; (4) insulin-dependent diabetes mellitus; (5) renal or hepatic impairment, including a history of alcoholism or hepatitis; and (6) treatment for recent malignancy. The new intervention will have to demonstrate that it has an acceptable long-term safety profile.

Scenario number two (Table II) explores the possibility that a novel intervention would be found to be equally effective as MTX. The new intervention could be used in any patient with any of the six factors described in scenario one. In addition, it now becomes more relevant for the physician and patient to explore the potential problems associated with the use of MTX versus those described with the new agent. It is important to consider that much of the data on MTX tolerability and toxicity, including the more recent focus on lung disease and the development of lymphomas, did not really emerge until the drug was in widespread use for a number of years. Just because a new agent has not demonstrated any serious toxicity over a period of one or two years does not mean that none will emerge over prolonged treatment intervals of 5 - 10 years or more.

Finally, the scenario of a novel agent which is superior to MTX deserves consideration. All of the issues with scenario two that apply to MTX are relevant here, except that their importance is somewhat diminished if the drug demonstrates superior efficacy. It is likely, however, that there will still be some patients who will not be comfortable either giving themselves injections or incurring significantly greater drug expense.

Nevertheless, it is self-evident that the therapeutic choices will never expand if we become too preoccupied with the paucity of long-term data on any new agent. This should not be a reason, in itself, for a new intervention not to be used. It is, however, reason for appropriate clinical caution when making therapeutic recommendations for a lifelong disease like RA. Some individuals may not wish to use a parenterally administered agent. The willingness of such patients to endure this inconvenience will be enhanced if it can be demonstrated that the short- and long-term toxicity associated with the use of these new drugs is preferable to the risk of taking MTX.

An additional factor dictating the patient's and physician's choice of drug is likely to be expense. Parenterally administered biotechnology agents are considerably more expensive than MTX. At the time of this writing, the increased expense of some new drugs is resulting in denials of insurance coverage for certain individuals with less generous insurance carriers. Society will have to decide whether the potential improved outcomes which could be associated with these new agents is worth the "up-front" expense. Long-term investigations of the utility and cost-effectiveness of new agents are needed to address this question. Long-term outcomes which include the incidence of elective joint arthroplasty, maintenance of functional status, employability, and earning capacity are needed. Cost savings derived from improvements in these parameters must be balanced against the immediate cost of the drugs themselves.

In summary, the new insights into the molecular basis for disease has led to the development of new therapeutic approaches that will be useful both by themselves and in combination with MTX. It is likely that virtually all of these agents will be used in combination with MTX owing to its present position as the dominant drug used to treat RA and its demonstrated long-term safety profile. There is also significant potential for new drugs which would hypothetically demonstrate modest or equivalent efficacy compared with MTX. A critical component of the profile of a new agent that is capable of assuming a viable long-term therapeutic position will be the demonstration of long-term tolerability.

References

1. KREMER JM, LEE JK: The safety and efficacy of the use of methotrexate in long-term therapy for rheumatoid arthritis. *Arthritis Rheum* 1986; 29: 822-31.
2. WEINBLATT ME, COBLYN JS, FOX DA, *et al.*: Efficacy of low-dose methotrexate in rheumatoid arthritis. *N Engl J Med* 1985; 312: 818-22.
3. WEINBLATT ME, WEISSMAN BN, HOLDSWORTH DE, *et al.*: Long-term prospective study of methotrexate in the treatment of rheumatoid arthritis: 84 month update. *Arthritis Rheum* 1992; 35:129-37.

4. FURST DE, ERIKSON N, CLUTE L, *et al.*: Adverse experience with methotrexate during 176 weeks of a long-term prospective trial in patients with rheumatoid arthritis. *J Rheumatol* 1990; 17: 1628-35.
5. KREMER JM: Safety, efficacy and mortality in a long-term cohort of patients with RA on methotrexate: Follow-up after a mean of 13.3 years. *Arthritis Rheum* 1997; 40: 984-5.
6. KREMER JM, LEE JK: A long-term prospective study of the use of methotrexate in rheumatoid arthritis: Update after a mean of 53 months. *Arthritis Rheum* 1988; 31: 577-84.
7. KREMER JM, PHELPS CT: Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis: Update after a mean of 90 months. *Arthritis Rheum* 1992; 35: 138-45.
8. WEINBLATT ME, KAPLAN H, GERMAIN BF, *et al.*: Low-dose methotrexate compared with auranofin in adult rheumatoid arthritis: A thirty-six-week, double-blind trial. *Arthritis Rheum* 1990; 33: 330-8.
9. WEINBLATT ME, TRENTHAM DE, FRASER PA, *et al.*: Long-term prospective trial of low dose methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 167-75.
10. KREMER JM, ALARCÓN GS, LIGHTFOOT RW, *et al.*: Methotrexate for rheumatoid arthritis: Suggested guidelines for monitoring liver toxicity. *Arthritis Rheum* 1994; 37: 316-28.
11. KREMER JM, FURST D, WEINBLATT ME, *et al.*: Significant changes in serum AST across hepatic histological biopsy grades: An analysis of 3 prospective cohorts on methotrexate therapy for rheumatoid arthritis. *J Rheumatol* 1996; 23:459-61.
12. ALARCÓN GS, KREMER JM, MACALUSO M, *et al.*: Risk factors associated with lung injury in methotrexate-treated rheumatoid arthritis patients: A multicenter, case-control study. *Ann Intern Med* 1997; 127: 356-64.
13. KREMER JM, ALARCÓN GS, WEINBLATT ME, *et al.*: Clinical, laboratory, radiographic and histopathologic features of methotrexate lung injury in patients with rheumatoid arthritis: A multi-center study with literature review. *Arthritis Rheum* 1997; 40: 1829-37.
14. MIOSSEC P, VAN DEN BERG W: Review: TH1/TH2 cytokine balance in arthritis. *Arthritis Rheum* 1997; 12: 2105-15.
15. O'DELL JR, HAIRE CE, ERICKSON N *et al.*: Treatment of rheumatoid arthritis with methotrexate, sulfasalazine and hydroxychloroquine, or a combination of these medications. *N Engl J Med* 1996; 334: 1287-91.
16. TUGWELL P, PINCUS T, YOCUM D *et al.*: Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. *N Engl J Med* 1995; 333: 137-41.
17. CRONSTEIN BN: Molecular therapeutics. Methotrexate and its mechanism of action. *Arthritis Rheum* 1996; 39: 1951-60.
18. KREMER JM: Possible mechanisms of action of methotrexate in patients with rheumatoid arthritis. *Br J Rheumatol* 1995; 34 (Suppl.): 26-9.
19. GEORGESCU L, QUINN GC, SCHWARTZMAN S *et al.*: Lymphoma in patients with rheumatoid arthritis: Association with the disease state or methotrexate treatment. *Semin Arthritis Rheum* 1997; 26: 794.
20. GRIDLEY G, MCLAUGHLIN JK, EKBOM A *et al.*: Incidence of cancer among patients with rheumatoid arthritis. *J Natl Cancer Inst* 1993; 85: 307-11.
21. WILLIAMS HJ, WARD JR, READING JC *et al.*: Comparison of auranofin, methotrexate, and the combination of both in the treatment of rheumatoid arthritis. A controlled clinical trial. *Arthritis Rheum* 1992; 35: 259-69.