



Low-dose methotrexate: anti-inflammatory or immunosuppressive?

METHOTREXATE'S VALUE for treating rheumatoid arthritis was first reported in 1951,¹ and the Cleveland Clinic experience was reported in 1980.² During the 1980s, methotrexate became a commonly used second-line agent for treating rheumatoid arthritis, even before its recent approval for this indication by the Food and Drug Administration. The reason for its popularity is simple: low-dose methotrexate is effective and well tolerated in patients with rheumatoid arthritis. However, the mechanism of action responsible for the observed clinical efficacy is not well defined. Even classification of the drug is controversial. Is methotrexate anti-inflammatory, immunosuppressive, or both?

ANTI-INFLAMMATORY EFFECTS

The relatively rapid onset of the clinical effects of methotrexate suggests an anti-inflammatory mechanism of action. Whereas other second-line agents such as gold salts require several months of administration before improvement is seen, methotrexate often exerts beneficial effects within weeks.

■ See Calabrese and associates (pp 232-241)

Also consistent with an anti-inflammatory mechanism of action, methotrexate mediates decreased synthesis of leukotriene B₄ and generation of superoxide as well as decreased chemotaxis for polymorphonuclear leukocytes and monocytes.³⁻⁵ Another mediator with proinflammatory properties, which also has links to the specific immune system, is interleukin-1; in vitro studies indicate that methotrexate can inhibit the functional activity of this cytokine.⁶ Changes in the activity of in-

terleukin-1, which could occur quickly in vivo, might partly explain the rapid phase of the observed clinical response. However, all of these studies of anti-inflammatory effects have been done in vitro or in mice, in some cases using high doses and prolonged incubations. Thus the in vivo relevance in patients with rheumatoid arthritis remains to be demonstrated.

EFFECTS ON IMMUNE FUNCTION

The immune system changes seen in treatment with methotrexate support a role for this agent as a modifier of immune response. Decreased antibody production has been observed,⁷ whereas levels of serum rheumatoid factor have been variously reported to be decreased^{8,9} or unchanged¹⁰ during methotrexate therapy. These variable results may be explained in part by the relatively insensitive titrating techniques used to measure rheumatoid factor.

A more sensitive radioimmunoassay method has demonstrated that in vitro synthesis of IgM-rheumatoid factor by peripheral blood mononuclear cells from rheumatoid arthritis patients decreases within 24 hours of the initial methotrexate dose.¹¹ In other studies that are in progress, we have observed declines in both the in vitro production and the plasma levels of IgM-rheumatoid factor in patients who were followed prospectively for 1 year after they started treatment with methotrexate.

These decreases in antibody and autoantibody production may result from a direct action of methotrexate on B cells or may be an indirect effect achieved by altering the number or function of relevant T-cell subsets. In fact, data can be cited to support all of these possible pathways for methotrexate action.

Inhibition of B-cell proliferation and antibody production in the presence of methotrexate¹² may be caused

by impaired ability of the B cell to produce purines and thus to synthesize RNA.¹³ Alternatively, effects on antibody production may be mediated by T cells, which exert controlling effects on the relevant B cells. Exposure of T cells to methotrexate in vitro decreases mitogen-induced cell proliferation,¹² whereas exposure in vivo in rats with streptococcal cell wall-induced arthritis enhances production of interleukin-2.¹⁴ Increased interleukin-2 synthesis is also consistent with enhanced in vitro antigen- and mitogen-induced proliferative responses of peripheral blood mononuclear cells from rheumatoid arthritis patients treated with methotrexate.¹⁰

Quantitative changes in T cells and T-cell subsets in patients treated with methotrexate have also been reported. The changes include increases in the relative numbers of total T cells (CD3) and helper T cells (CD4).¹⁰ The study by Calabrese and associates in this issue extends these observations to the examination of other T-cell subsets that have specifically defined functions.

At baseline, the rheumatoid arthritis patients studied had a significant deficit in the CD4⁺2H4⁺ suppressor/inducer and CD8⁺C11b⁺ suppressor/effector T-cell subpopulations. Treatment with methotrexate partly normalized these subsets. Since T-suppressor/inducer and T-suppressor/effector cells in turn influence levels of antibody synthesis, these findings suggest that methotrexate may mediate decreased antibody and autoantibody synthesis through quantitative changes in the relevant T-cell subsets.

WHY DOES IT MATTER?

Determining whether methotrexate has immunosuppressive or anti-inflammatory properties is of more than academic interest. A better understanding of underlying mechanisms of action would help determine where methotrexate most logically fits in the therapeutic scheme.

If methotrexate is found to have a relatively rapid onset of action along with anti-inflammatory effects, it may be useful to combine it with a slow-acting agent with immunosuppressive properties. Clinical trials in progress using methotrexate in combination with gold or azathioprine may help answer this question.

Immunosuppression mediated by methotrexate could have lasting effects on the course of the disease, even though some clinical effects of methotrexate reverse rapidly after it is discontinued.¹⁵ For example, no studies have examined whether the observed immunologic changes are reversed when treatment is stopped. Controlled observations over long periods are also needed to confirm the suggestion that methotrexate may alter such measurable effects of the disease as radiographic damage.¹⁰

Despite the unanswered questions, methotrexate will likely remain an important component of therapy for rheumatoid arthritis for years to come.

NANCY OLSEN, MD
Division of Rheumatology and Immunology
Vanderbilt University
Nashville, Tennessee 37232

REFERENCES

- Grubner R, August S, Ginsberg V. Therapeutic suppression of tissue reactivity; II. Effect of aminopterin in rheumatoid arthritis and psoriasis. *Am J Med Sci* 1951; 22:176-182.
- Wilke WS, Calabrese LH, Sherbel AL. Methotrexate in the treatment of rheumatoid arthritis; pilot study. *Cleve Clin Q* 1980; 47:305-309.
- Sperling R, Larkin J, Coblyn J, Austen KF, Weinblatt M. Methotrexate decreases leukotriene B₄ production in rheumatoid arthritis. *Arthritis Rheum* 1989; 32:543.
- Nesher G, Moore TL. Effect of methotrexate on chemotaxis and superoxide production of normal monocytes. *Arthritis Rheum* 1989; 32:S60.
- Suarez CR, Pickett WC, Bell DH, McClintock DK, Oronsky AL, Kerwar SS. Effect of low dose methotrexate on neutrophil chemotaxis induced by leukotriene B₄ and Complement C5a. *J Rheumatol* 1987; 14:9-11.
- Segal R, Mozes E, Yaron M, Tartakovsky B. The effects of methotrexate on the production and activity of interleukin-1. *Arthritis Rheum* 1989; 32:370-377.
- Andersen PA, West SG, O'Dell JR, Via CS, Claypool RG, Korzin BL. Weekly pulse methotrexate in rheumatoid arthritis. Clinical and immunologic effects in a randomized double-blind study. *Ann Intern Med* 1985; 103:489-496.
- Williams HJ, Willkens RF, Samuelson CO Jr, et al. Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis: a controlled clinical trial. *Arthritis Rheum* 1985; 32:721-730.
- Weinstein A, Marlowe S, Korn J, Farouhar F. Low-dose methotrexate treatment of rheumatoid arthritis: Long-term observations. *Am J Med* 1985; 79:331-337.
- Weinblatt ME, Trentham DE, Fraser PA, et al. Long-term prospective trial of low-dose methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1988; 31:167-175.
- Olsen NJ, Callahan LF, Pincus T. Immunologic studies of rheumatoid arthritis patients treated with methotrexate. *Arthritis Rheum* 1987; 30:481-488.
- Olsen NJ, Murray LM. Antiproliferative effects of methotrexate on peripheral blood mononuclear cells. *Arthritis Rheum* 1989; 32:378-385.
- Rosenthal GJ, Weigand GW, Germolec DR, Blank JA, Luster MI. Suppression of B cell function by methotrexate and trimetrexate: evidence for inhibition of purine biosynthesis as a major mechanism of action. *J Immunol* 1988; 141:410-416.
- Ridge SC, Rath N, Galivan J, Zabriskle J, Oronsky AL, Kerwar SS. Studies on the effect of D-penicillamine, gold thioglucose and methotrexate on streptococcal cell-wall arthritis. *J Rheumatol* 1986; 13:895-898.
- Furst DE, Kremer JM. Methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1988; 31:305-314.