

Rostrums

Recent trials of low-dosage methotrexate in chronic steroid-dependent asthma have engendered considerable interest and debate. It is still too early to say whether the variable steroid-sparing effects in the reports to date will be found in other controlled studies underway. However, I felt that our readers would be interested in the following two Rostrum articles. In the first, Dr. Mullarkey, an early proponent of methotrexate use in asthma, gives his impressions of the clinical effects of this drug. In the second article, Calderon et al. review some knowledge of the biological actions of methotrexate.—Burton Zweiman, MD, *Editor*.

Methotrexate and asthma

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The article in the current issue of the JOURNAL by Dyer et al.¹ is the third placebo-controlled study establishing the efficacy of low-dose methotrexate as an alternative to toxic doses of corticosteroids in the treatment of severe bronchial asthma.^{2, 3} An additional study has demonstrated continued efficacy and acceptable toxicity when methotrexate is used for up to 2 years to treat asthma.⁴ These studies suggest that we may be on the threshold of a new era in the treatment of BA. In retrospect, this is hardly surprising. Rheumatologists were the first physicians to use corticosteroids to suppress chronic inflammation in human disease and the first to realize its dangers. This early understanding of corticosteroids and their limitations led to the initial development of safer anti-inflammatory agents. In 1951, Gubner et al.⁵ used aminopterin, a precursor of methotrexate, to successfully treat patients with RA and psoriasis. They chose this alternative to corticosteroids because of "the unavailability of cortisone and adrenocorticotrophic hormone, and their untoward effects with protracted administration." This continuing concern by rheumatologists for the toxicity of cortisone led to the development of other alternates to cortisone in the treatment of arthritis. Antimalarials, gold salts, penicillamine, and sulfasalazine were early entries in the contest to replace cortisone in treating chronic inflammatory disease of the joints and skin. With years of experience, dosages and schedules of administration for each of these drugs has undergone extensive revision, minimizing toxicity, while efficacy has been maintained or increased. Some agents initially tried have been discarded, and other agents, such as metho-

Abbreviations used

BA: Bronchial asthma

RA: Rheumatoid arthritis

trexate, have assumed a major role in the management of RA.⁶

Paralleling these observations in rheumatology, clinicians treating asthma in the 1950s and 1960s realized the importance of inflammation in the pathogenesis of asthma. Their attempt to control inflammation with immunosuppressive agents was often successful and was based on the then popular assumption that inflammation was the result of an inappropriate antigen-antibody reaction deleterious to the host.⁷⁻¹⁰ The unacceptable toxicities noted with the doses used by these early investigators led to a plea to end all further investigation of such agents in the treatment of non-malignant disorders.¹¹ Fortunately, clinical rheumatologists and dermatologists elected to continue to refine and expand their initial observations. During this same period, clinicians in the United States, France, and Japan reported success in open trials of antimalarials and gold in the treatment of BA.¹²⁻¹⁴ The use of methotrexate as an anti-inflammatory agent in the treatment of asthma evolved naturally from the long and often successful search for effective and safer alternatives to corticosteroids.

The success of methotrexate as steroid sparing in asthma raises two sorts of questions: questions related to the specifics of drug use and questions that address our fundamental assumptions about asthma therapy.

Regarding the specifics of drug use, who should receive this drug? Clearly, subjects with asthma who have developed corticosteroid side effects despite maximal attempts to reduce cortisone should benefit from a trial of methotrexate. As in the treatment of rheumatologic and dermatologic diseases, the risk-

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benefit profile of methotrexate is preferable to that of long-term prednisone at a dose of 10 mg/day. Methotrexate is neither mutagenic nor oncogenic. It is less efficiently metabolized in patients older than 50 years of age.¹⁵ These observations, plus the devastating morbidity of steroid dependence in younger subjects and success of methotrexate as steroid sparing in juvenile RA^{16, 17} make its consideration in younger patients reasonable.

Who should use this drug? Because of the complexity involved in properly evaluating and treating severe asthma, the use of low-dose methotrexate should be restricted to specialists. Methotrexate should be used only after the treating physician acquires thorough familiarity with this well-known medication. The pharmacology and guidelines for its use are adequately covered in several reviews.¹⁸⁻²⁰ It is unknown how long to continue treatment. In our experience, stopping methotrexate treatment within the first month of stopping prednisone has led to exacerbation of disease. We now stop methotrexate 6 months after stopping prednisone. Although relapse has occurred in some patients, other patients have not required regular prednisone for more than 2 years. It is very important that patients continue with their usual asthma medications, both while they are attempting to reduce corticosteroids and after stopping methotrexate. In our experience, plateaus in efficacy of methotrexate have usually been traced to poor compliance with routine asthma medications, particularly inhaled corticosteroids. A response to methotrexate does not remove the need for periodic bursts of prednisone. Methotrexate is a slow-acting drug that appears to reset the level of inflammation and hence the requirement for maintenance corticosteroids. Exacerbations of asthma must still be treated early and aggressively with prednisone. Patients responding to methotrexate respond rapidly to doses of prednisone that were ineffectual before the use of methotrexate and tolerate more rapid reductions in corticosteroids than before methotrexate treatment. Although response to methotrexate appears high, some patients may not respond for as long as a year and other patients may not respond at all. Clearly, there is a need for the development of additional "steroid-sparing" drugs.

Finally, the effectiveness of low-dose methotrexate in corticosteroid-dependent BA raises a number of fundamental questions regarding our current approach to the treatment of asthma. If mild disease causes morphologic change in the bronchi²¹ and prolonged disease is associated with declining pulmonary function,²² then when should anti-inflammatory agents be used in asthma care? Should we restrict ourselves to the use of the mild anti-inflammatory drugs, cromolyn

and inhaled corticosteroids? Such delays will continue the pattern whereby steroid dependence develops in some patients and the loss of pulmonary function occurs in many patients. Are we, as some rheumatologists have suggested, "saving our best drugs for last?"²³ Would it be more reasonable to carefully examine the risk-benefit ratio and bring our most potent drugs to bear sooner in this serious disease? These questions are sure to provoke strong and often emotional responses, but given our current knowledge of the pathophysiology and natural history of asthma, the time to begin to consider these issues is now.

Methotrexate is preferable to the toxic doses of prednisone once used to treat asthma; the evidence is incontrovertible; the alternatives are unacceptable. By virtue of our training and the concentration of our efforts, allergists are the natural leaders in asthma care. We must therefore assert this leadership by defining for other physicians the role of methotrexate and future anti-inflammatory agents in the management of this prevalent and often terrible disease.

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Methotrexate in bronchial asthma

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MTX, a folic acid antagonist, has antineoplastic activity based on the inhibition of DHFR, which reduces folate to tetrahydrofolate. Inhibiting the formation of tetrahydrofolate causes a major disruption of cellular metabolism by inducing an acute intracellular deficiency of folate coenzymes, particularly in transmethylation pathways. The *de novo* synthesis of purine nucleotides and of thymidylate ceases with subsequent interruption of the synthesis of DNA and RNA (as well as other vital metabolic reactions).¹

MTX has been used in high doses (50 to 150 mg/week) as a cytotoxic agent in treatment of neoplasms. Lower dosages (5 to 25 mg/week) have been an effective treatment in inflammatory diseases, such as psoriatic arthritis, RA, polymyositis, and systemic lupus erythematosus. MTX has also been effective and safe in low doses (7.5 to 50 mg/week) for severe asthma as an adjunct to glucocorticoids.

Although the mechanism of action of MTX in asthma has not been established, it is unlikely that it depends on inhibition of DHFR, given that (1) it re-

Abbreviations used

MTX: Methotrexate
DHFR: Dihydrofolate reductase
PMNL: Polymorphonuclear leukocyte
RA: Rheumatoid arthritis
LTB₄: Leukotriene B₄
EOS: Eosinophil
IL-1: Interleukin-1

tains its anti-inflammatory action at doses of 15 mg/week even after supplementation with folinic acid (1 mg of folinic acid per 1 mg of MTX)² and (2) DHFR is either absent or is present at very low concentrations in leukocytes,³ which are the major cell types in the inflammation of chronic asthma, and (3) low-dose MTX does not cause leukopenia.

Alternatively, since asthma is an inflammatory disease, the following pharmacologic actions of MTX, observed in the laboratory and also in patients with psoriasis or RA treated with low doses of MTX, may explain its mechanism of action in asthma: (1) inhibition of chemotaxis of PMNLs,⁴⁻⁸ (2) inhibition of activity of IL-1,⁹ and (3) inhibition of histamine release by basophils.¹⁰

EVIDENCE AND COMMENTS

Inhibition of chemotaxis of PMNLs

Ternowitz and Herlin⁴ studied chemotaxis of PMNLs and monocytes in three groups of individuals: (1) 15 patients with psoriasis receiving long-term

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