ARTHRITIS & RHEUMATISM
Vol. 58, No. 11, November 2008, pp 3279–3282
DOI 10.1002/art.24032

Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and www.interscience.wiley.com

EDITORIAL

Methotrexate Treatment of Rheumatic Diseases: Can We Do Better?

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It is very likely that methotrexate (MTX) is the best-studied drug the world has ever seen. Indeed, this statement was undoubtedly true more than 25 years ago, prior to the widespread use of MTX for any indication except those related to oncology and dermatology. Hundreds, if not thousands, of peer-reviewed publications in the medical and scientific literature have described the clinical and metabolic effects of MTX on a variety of normal and tumor-specific tissues. Its actions have been described in detail in a variety of systems (1). Of course, in the past few decades, hundreds of articles have been published describing the effects of MTX in rheumatic diseases.

MTX became recognized as the single most effective agent for the treatment of rheumatoid arthritis (RA) in North America in the 1980s and in Europe in the 1990s. MTX is widely acknowledged to be the mainstay, or cornerstone, of treatment of patients with RA (2,3). It is now also recognized that combination treatment with MTX plus biologic agents is more effective than is treatment with either of these modalities alone (4,5).

It is therefore somewhat surprising that further insights could be derived that could help in understanding the fundamental behavior of this ubiquitous agent, which has been used for so long. However, in the last several years, we have learned that sulfasalazine actually inhibits the uptake of MTX at the reduced folate carrier (6), and that hydroxychloroquine may inhibit the metabolism of MTX to its less active metabolite, 7-hydroxy-MTX (7). In addition, the aldehyde oxidase enzyme that catalyzes the conversion of MTX to 7-hydroxy-MTX has distinct phenotypes, which were recently described (8). When considered together, these observations permit plausible insights into previously described clinical observations that the combination of MTX and hydroxychloroquine is more effective than the combination of MTX and sulfasalazine (9).

Further insights to explain some already-observed clinical behaviors of MTX are now provided by Dalrymple and colleagues in this issue of *Arthritis & Rheumatism* (10). Dalrymple et al describe the chronology of MTX polyglutamation in the circulating red blood cells (RBCs) of patients with RA who began or discontinued treatment with MTX. As those authors explain, MTX is retained within the cell only in the polyglutamated form, in which successive glutamic acid moieties are added by the enzyme folylpolyglutamate synthetase (FPGS) (Figure 1). In the absence of polyglutamation, MTX is thought to quickly efflux from the cell. The glutamic acid moieties (up to 5) are added successively, in a relatively slow process. As has also been described by other investigators, the most prevalent species of polyglutamate observed by Dalrymple et al was MTX polyglutamate 3 ($MTXGlu_3$) (37%), with $MTXGlu_2$ comprising 21% of total MTXGlu, and $MTXGlu_4$ and $MTXGlu_5$ comprising 11% and 6% of the total, respectively (10).

RBC MTXGlus accumulate in RBC progenitor cells prior to release from the bone marrow into the circulation, and these concentrations are thought to be representative of the MTXGlu concentration in other tissues. Because circulating RBCs comprise a continuously changing population, RBC MTXGlu concentrations will reflect the dynamics of MTX exposure in the marrow of these cells prior to their release. RBC MTXGlu total concentrations have been described as

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Submitted for publication June 30, 2008; accepted in revised form August 11, 2008.

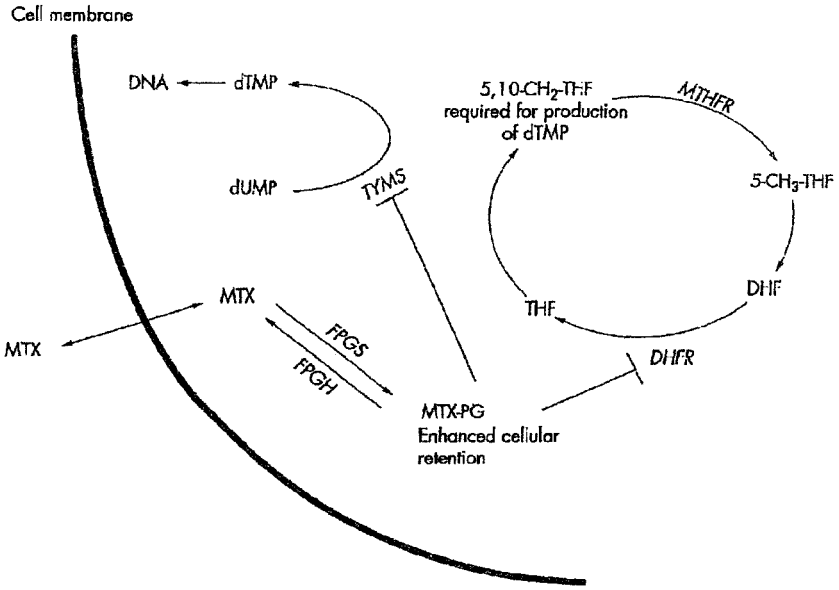

Figure 1. Basic metabolic processes associated with methotrexate (MTX) cellular uptake and polyglutamation (PG). Progressive glutamic acid moieties are added slowly by the enzyme folylpolyglutamate synthetase (FPGS) and are removed by folylpolyglutamate hydrolase (FPGH). Other folate antagonists, such as aminopterin, are polyglutamated more efficiently than is MTX. The figure does not depict the entire range of the intracellular effects of MTX. dTMP = thymidylate monophosphate; 5,10-CH_2-THF = 5,10-methylene tetrahydrofolate; MTHFR = methylene tetrahydrofolate reductase; dUMP = deoxyuridine monophosphate; TYMS = thymidylate synthase; DHFR = dihydrofolate reductase.

correlating with the overall clinical response in patients with RA who are receiving MTX (11).

As described by Dalrymple et al, 12.5 weeks were required to achieve an accumulation half-life of $MTXGlu_3$, and 41.2 weeks were required to achieve steady state once the final MTX dose was administered (10). After treatment with MTX is stopped, MTXGlu will remain in tissue for relatively prolonged periods of time. As reported by Dalrymple et al, the elimination half-life of $MTXGlu_3$ was 4.3 weeks, and a full 10 weeks (range 2–>21 weeks) were required until it was undetectable (10). An inspection of the concentration-time profiles of $MTXGlu_3$ presented by the authors reveals a steady accumulation in a patient in whom no dose changes occurred, and this accumulation does not completely plateau until ~35 weeks after administration of the final dose. A similar time course is seen in the concentration-time profile of both $MTXGlu_3$ and MTX total ($MTXGlu_{1–5}$) for a patient whose dose is increased incrementally during the first months of treatment through week 12.

It is very tempting to try to connect some of the dots from previously described MTX clinical behavior using these new insights into cellular mechanisms. The clinical effects of MTX do not reach a plateau until 6 months (12,13), which corresponds well to the 41.2 weeks required to reach steady state concentrations of $MTXGlu_3$ reported by Dalrymple et al (10). Patients discontinuing treatment with MTX do not experience a disease flare until approximately 1 month after stopping treatment (14), which corresponds to the elimination half-life of 4.3 weeks for $MTXGlu_3$ described by Dalrymple et al (10).

What has been learned from these new observations that could help clinicians in treating patients? How could practitioners improve upon the clinical effects of MTX? As Dalrymple et al propose, treatment could start with a higher initial weekly dose of MTX, so that less time would be required to reach steady state. In addition, the higher weekly dose of MTX could be administered parenterally so that bioavailability is enhanced (15,16). However, even with these maneuvers, it

is unlikely that the basic metabolic processes associated with MTX cellular uptake and polyglutamation (Figure 1) can be altered. As Dalrymple et al describe, the process of the addition of successive glutamic acid moieties by FPGS is slow and at least partially dependent on multiple other genetic polymorphisms in the reduced folate carrier and FPGS itself (17,18). In addition, multiple other single-nucleotide polymorphisms (SNPs) have now been described in folate pathway SNPs affected by MTX (19). Thus, the ability to change the metabolism of MTX is limited primarily by genetic polymorphisms that, at present, are considered unalterable.

However, other folate antagonists have been developed and have been available for some time. Edatrexate, pralatrexate, and aminopterin are folate antagonists that are polyglutamated more efficiently (i.e., more quickly) than is MTX (20,21). Aminopterin also accumulates to a lesser extent in the central nervous system (CNS) and appears to have less CNS toxicity in cancer patients and could also have less CNS toxicity when used weekly in patients with rheumatic diseases (20). These agents have not yet been adequately studied for the treatment of patients with chronic rheumatic diseases, although Alarcon et al have reported the effects of 10-deazaaminopterin, a related compound, in a small study of patients with RA (22).

It is therefore possible that the clinical profile of one of these other antifolates could be enhanced relative to that of MTX, perhaps without increased toxicity. Many questions must be answered if other folate antagonists are to be seriously considered in place of MTX, including not only safety, but also the rapidity and quality of the clinical response that is achieved.

MTX is a very good, if not superb, drug for the treatment of patients with RA. However, as new insights into the well-described clinical effects of MTX emerge, a more refined and sophisticated manipulation of intracellular folate metabolism could become feasible. It is possible that MTX may not actually be the ideal folate antagonist for patients with rheumatic disease, in spite of its rich, decades-long clinical history. Although impediments to the clinical development and study of new antifolate compounds abound, these efforts are certainly reasonable and should continue. It is possible that there are yet more efficient ways to inhibit folate metabolism in patients with rheumatic diseases in order to achieve the best, most rapid, and safest possible clinical results.

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