

The Role of Concomitant Methotrexate in Biologic Therapy for Rheumatoid Arthritis

Eric M. Ruderman, M.D.

Abstract

From the first use of biologic therapy for the management of rheumatoid arthritis, methotrexate (MTX) has been commonly used as co-therapy. There are a number of mechanistic reasons why MTX may improve the efficacy of biologics, including reduced antigenicity as well as reduced clearance of the biologic agent. Clinical trial data for tumor necrosis factor inhibitors and for other biologic agents does suggest added efficacy when these agents are used in combination with MTX. One exception may be the interleukin-6 receptor antibody tocilizumab, for which there is some data to suggest that monotherapy may be as effective as combined therapy with MTX. Post-marketing registry data also supports the concomitant use of MTX with biologics, with evidence for greater efficacy and longer persistence on treatment when compared with monotherapy.

From the first approval of biologic therapy for rheumatoid arthritis (RA) nearly 15 years ago, the question of concomitant methotrexate (MTX) use has been an important issue for clinicians. Early trials focused on the use of biologics in a MTX inadequate responder population, and MTX was continued per protocol in most cases. Subsequent trials included several with designs that evaluated the use of biologic therapy both with and without concomitant MTX in the same study. As these agents have become an important part of the standard of care for RA, data collected from registry studies has also helped inform clinicians regarding the value of concomitant MTX with respect to the response to, and persistence of, biologic therapy. This manuscript will

review the published evidence for added efficacy of biologic therapy with concomitant MTX and will also examine the question of whether any such benefit applies equally to all biologic agents. The impact of concomitant use on the safety of biologic therapy will be reviewed elsewhere in this supplement.

There are several potential mechanisms by which MTX might improve response to biologic therapy in RA, from abrogation of antibody development to the biologic, to inhibition of clearance of the biologic, to synergism of effects on the disease process itself. The impact of MTX on the development of anti-biologic antibodies is a greater issue for some agents than for others. In the early trials of infliximab in RA, it became clear that, with ongoing therapy, the duration of response to this chimeric, and thus potentially highly antigenic, antibody tended to become shorter with each subsequent dose. Methotrexate proved useful at reducing the development of anti-infliximab antibodies, thus increasing the sustainability of the response to the infliximab.¹ In the case of infliximab, there is also data to suggest that other immunosuppressive agents may serve the same purpose when MTX cannot be used. Similar observations have been reported in the treatment of inflammatory bowel disease, where early use of infliximab monotherapy has given way to a standard of care that includes concomitant immunosuppressives.

Interestingly, infliximab is typically administered alone in ankylosing spondylitis, a disease in which the lack of demonstrable therapeutic benefit from MTX makes it more difficult to justify the addition of this drug to a biologic regimen. When used with infliximab, it is not fully clear how much MTX is required to impact the development of antibodies; it may be that doses lower than those commonly used to treat RA are sufficient. In an animal model of RA using human RA pannus implanted in SCID mice, infliximab alone was sufficient to suppress synovial inflammation, but

Eric M. Ruderman, M.D., is Professor of Medicine, Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Correspondence: Eric M. Ruderman, M.D., Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois 60611; e-ruderman@northwestern.edu.

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the addition of MTX was necessary to also inhibit bone destruction.²

While it would seem likely that the value of MTX in reducing anti-biologic antibodies would be greater for more highly antigenic agents, MTX has also been shown to reduce antibody development and improve response to the fully human antibody adalimumab.³ In the case of adalimumab, there may be other mechanisms at play as well, as pharmacokinetic data has shown that MTX reduces clearance of adalimumab. Regardless of the mechanism, clinical trial data has clearly demonstrated that concomitant use of MTX improves response to adalimumab. In the PREMIER trial, the addition of adalimumab to MTX therapy proved more effective than switching to adalimumab monotherapy for all measures of response, including radiographic progression.⁴ In the GO-FORWARD trial with golimumab, another fully human monoclonal antibody, the combination of golimumab and MTX proved more effective than golimumab alone in a similar population of MTX inadequate responders.⁵

The PREMIER trial and the GO-FORWARD trial both demonstrated the value of adding a TNF inhibitor to the therapy of patients who were inadequate responders to MTX alone. Similar clinical trial evidence supports the benefit of *initial* therapy with etanercept plus MTX compared with etanercept alone. In the TEMPO trial, patients not currently being treated with MTX and who had not previously demonstrated lack of response to this drug, were shown to have a greater response to the combination than to etanercept monotherapy; in this trial as well, the benefit of the combination extended to structural progression as well as clinical response.⁶ In an alternate trial design in the JESMR study, patients with active disease despite MTX were either switched to etanercept or had etanercept added to their MTX (at a dose of just 6 to 8 mg/week in this Japanese study). The clinical response to the combination was greater at both 24 and 52 weeks, and radiographic progression was decreased with the combination, leading the investigators to suggest that MTX be continued whenever etanercept is started.^{7,8} While the effectiveness of certolizumab pegol, the fifth approved TNF inhibitor, as monotherapy has been published, there is no data directly comparing this approach to the use of certolizumab with MTX.

The availability of data on the addition of MTX to therapy with biologics other than TNF inhibitors is mixed. For abatacept, as with certolizumab, there is data on the efficacy of this agent as monotherapy and with concomitant MTX, but no data directly comparing the two approaches. Rituximab, on the other hand, appears to be more effective when administered concurrently with MTX. In a study of RA patients with active disease despite MTX, a single course of rituximab was given either alone or in combination with MTX or cyclophosphamide.⁹ All three dosing strategies for rituximab were superior to simply continuing MTX. Although the study was not powered to show a difference between the two, rituximab plus MTX showed a

trend towards greater efficacy than rituximab monotherapy, particularly at 48 weeks, when the therapeutic effect of the rituximab appeared to wane in the monotherapy arm. Like infliximab, rituximab is a chimeric antibody, although there was no suggestion in this trial that the additive benefit of MTX was attributable to a reduction in the development of anti-chimeric antibodies, as this protocol did not examine repeat dosing. Instead, this trial suggested that the addition of MTX therapy was able to extend or sustain the therapeutic response to rituximab.

The value of concomitant MTX therapy added to tocilizumab therapy in RA is somewhat less clear. In the ACT-STAR trial, designed primarily as a safety study, monotherapy with tocilizumab 8 mg/kg appeared to be as effective as tocilizumab 4 mg/kg or 8 mg/kg in combination with MTX.¹⁰ However, this was not a randomized study. Subjects receiving active monotherapy with an alternate biologic at screening were *assigned* to the monotherapy arm, making it impossible to truly compare the two treatment approaches. In the ACT-RAY trial, patients with an inadequate response to MTX were randomized to the addition of tocilizumab 8 mg/kg to their MTX or switching to tocilizumab monotherapy. In this study, there was no difference between the two groups in achieving the primary endpoint, DAS28-ESR remission, or in EULAR good/moderate or ACR 20/50/70 responses; however, the percentage of patients achieving DAS28 low disease activity was statistically greater in the combination arm.¹¹ Subsequent clinical trials, reported to date in abstract form only, have suggested that the response to tocilizumab monotherapy *may* be comparable to the response to tocilizumab plus MTX, which could conceivably make tocilizumab a more attractive biologic in situations where MTX is impractical or contraindicated.

While clinical trials can provide useful information about drug safety and efficacy, they may be less helpful for assessing clinical strategies, such as combination therapy with MTX, especially when there are few trials with direct comparisons between monotherapy and combination therapy. One approach to evaluating this question is to examine the response to, and persistence of, treatment in large cohorts of patients, where one can presume that earlier discontinuation of therapy may relate either to lack of efficacy or to safety issues.

In the British Society for Rheumatology Biologics Register, the use of concomitant MTX was found to be associated with a numerically greater response to both etanercept and infliximab, although, interestingly, the difference was only significant for etanercept. In this analysis, the likelihood of achieving clinical remission with the etanercept and MTX combination was 12% versus 5% with etanercept alone.¹² For infliximab, though, the difference was only 8% versus 7%.

The South Swedish Arthritis Treatment Group is a large, observational cohort of RA patients treated with a structured clinical protocol. In this cohort as well, combination therapy

with infliximab or etanercept and MTX was associated with greater response at 3 months follow-up and lower rates of discontinuation than monotherapy with either drug.^{13,14} Discontinuation due to adverse events was responsible for the greatest difference in persistence between monotherapy and combination for both drugs in this study; more treatment failures were seen with infliximab monotherapy but not with etanercept monotherapy. This cohort also included patients treated with adalimumab, but the number receiving adalimumab at the time of the analysis was too low to draw any meaningful conclusions.

The Italian GISEA registry and the Danish DANBIO registry also include patients treated with adalimumab, etanercept, and infliximab. An analysis of the DANBIO registry found differences in response and likelihood of drug withdrawal between the three TNF inhibitors; for the group as a whole, concomitant MTX therapy was associated with a greater likelihood of achieving a EULAR good response but not with other measures of response.¹⁵ The DANBIO analysis did not specifically look at the impact of MTX on treatment persistence. In the GISEA registry, which also found differences in retention rates between the three drugs, the greatest predictor of persistence on therapy for all three was the use of concomitant MTX.¹⁶

Finally, a recent systematic review of persistence rates with TNF inhibitors, while acknowledging the challenges of comparing discontinuation rates across studies, found that persistence on therapy was generally greater when TNF inhibitors were combined with MTX therapy.¹⁷

Because of their relatively recent availability and limited use, especially in Europe, from where much of the registry data originates, there is little published data on the impact of MTX on therapeutic persistence with certolizumab, golimumab, or the non-TNF inhibitor biologic therapies. One exception to this is found in a recent retrospective study of German patients treated with TNF inhibitors (N = 128) or tocilizumab (N = 126).¹⁸ There was a trend toward higher withdrawal rates with etanercept monotherapy compared with tocilizumab monotherapy in this study, which could reflect the clinical trial data suggesting that tocilizumab may be relatively more effective as monotherapy than TNF inhibitors; however, the number in each group was far too small to draw any firm conclusions.

While registry studies such as these can provide potentially useful information on the durability of therapy, their results must be interpreted with caution. Such observational studies are subject to significant potential bias; differences in outcomes may be just as easily due to differences between the patients selected for the various treatment regimens as to differences in safety and efficacy between treatments or treatment combinations. Nevertheless, the consistent finding from all of these analyses is that, for TNF inhibitor therapy, concomitant MTX is associated with greater efficacy and longer persistence on therapy.

In sum, the bulk of the evidence suggests that the addi-

tion (or continuation) of MTX therapy with TNF inhibitor therapy results in generally greater efficacy, although the mechanism for this observation has not been firmly established. Similar conclusions can be drawn from registry data suggesting longer treatment persistence with the combination. Treatment persistence may be due either to greater efficacy or fewer adverse events; this latter outcome may, itself, be linked to greater control of disease activity. The minimal dose of MTX necessary to confer this benefit is unknown, although the JESMR study, in which the mean dose was only 8 mg, may suggest that it is less than the usual therapeutic dose of 15 to 20 mg. The impact of concomitant MTX therapy on response to biologics other than TNF inhibitors, including the possibility that tocilizumab may be as effective as monotherapy as in combination, is less clear. Ongoing data being collected from registries and other clinical cohorts may help answer these questions.

Disclosure Statement

Eric M. Ruderman, M.D., is a consultant for AbbVie, Amgen, BMS, Celgene, Janssen, Lilly, Medac, Pfizer, and Vertex, and has provided paid expert testimony for Pfizer.

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