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Conventional DMARD Options for Patients with a Suboptimal Response to Methotrexate

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ABSTRACT. Methotrexate (MTX) is one of the disease modifying antirheumatic drugs (DMARD) commonly used to treat rheumatoid arthritis (RA). However, MTX therapy alone rarely results in remission and frequently does not even produce 50% improvement. Therefore, over the course of their disease, many patients will require additional therapy to manage their clinical symptoms. A number of treatment options have proven effective for such patients, most of which entail the continuation of MTX therapy and the addition of other DMARD. Although the combination of MTX and hydroxychloroquine (HCQ) is the one most commonly used in the US, many clinicians (particularly in Europe) prefer the combination of MTX and sulfasalazine. In addition, excellent data now exist for the triple combination of MTX, HCQ, and sulfasalazine in patients who have had a suboptimal response to MTX, as well as in those with early or well established disease. Other combinations, including MTX + cyclosporine or leflunomide, have also been helpful in some patients. Most recently, the tumor necrosis factor blockers, etanercept and infliximab, have successfully been used to treat a number of patients resistant to MTX. The combination of MTX with DMARD or biological agents with different mechanisms of action greatly expands the treatment options for patients with RA. (J Rheumatol 2001;28 Suppl 62;21–26)

Key Indexing Terms:
RHEUMATOID ARTHRITIS METHOTREXATE SUBOPTIMAL RESPONSE
DISEASE MODIFYING ANTIRHEUMATIC DRUGS COMBINATION THERAPY

This paper presents 2 case studies that illustrate some of the challenges when using the disease modifying antirheumatic drug (DMARD), methotrexate (MTX), to treat patients with rheumatoid arthritis (RA). The first case is typical of the patients we commonly encounter in our clinical practice in North America, while the second represents a more complex treatment dilemma. Although brief, these cases are used to initiate a discussion of treatment options for an important subset of patients with RA: those with a suboptimal response to MTX.

CASE 1. A SUBOPTIMAL RESPONSE TO MTX

A 49-year-old female with erosive, seropositive RA had been taking MTX 15 mg/wk PO for 4 months. When she returned to the clinic for a followup visit, she reported an increasing incidence of nausea and occasional mouth sores. She also continued to have 2+ synovitis in multiple joints. She started 2 mg/day of folic acid and 7.5 mg/day of prednisone. The dose of MTX was increased over 3 weeks to 25 mg/week and then switched to subcutaneous administration. Nevertheless, when she returned to the clinic in 2 months, she continued to have 2+ synovitis in multiple joints. The patient was now considered a candidate for combination DMARD therapy.

Improving the Response to MTX. The management of patients with RA remains a clinical challenge, since there are few instances in which one knows which drug will best serve a given patient. While it is possible for us to predict which patients with RA will do poorly, there are few factors that we can currently use to predict differentially which patients will respond to specific therapies. One of the main goals in this field therefore, is to identify predictors of differential response. In the absence of such benchmarks, we are forced to rely heavily on empiric DMARD for the initial treatment of most patients with RA.

At present, MTX is the most widely prescribed first line DMARD in the US due to its efficacy, good tolerability, and sustained response. However, approximately one-third of patients fail to respond to oral MTX and will require additional therapy. On the other hand, about one-third of these nonresponders will respond if switched to parenteral therapy. It has therefore become increasingly evident that the therapeutic outcome with MTX depends on multiple factors. For example, has an effective dose of this drug been prescribed for a given patient? Was the best titration schedule used? Is the drug being administered via the most optimal route? And can the outcome be improved (i.e., less toxicity) through the use of folate replacement?

These questions are germane in light of the fact that a new subset of patients with RA has emerged, which comprises those who have a suboptimal response to MTX. The definition

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of what, exactly, constitutes a suboptimal responder varies widely from study to study. In general, patients should be considered to have had a suboptimal response if they continue to have substantial disease activity, despite the use of 20 to 25 mg of MTX given subcutaneously or intramuscularly once per week. Therefore, the first step in treating the patient described in the present case study was to determine if she had had a suboptimal response to MTX. Since she was receiving only 15 mg/week of oral therapy, she was switched to subcutaneous dosing and the dose was pushed to 25 mg/week.

MTX can be given either orally, subcutaneously, or intramuscularly. Subcutaneous dosing is common in the US, while the intramuscular route is more common in Europe. The absorption following oral administration is variable, ranging from a low of 20 to a high of 95% (mean, ~80%), whereas the absorption following subcutaneous dosing is similar to that after intramuscular dosing[1-3]. These pharmacokinetic properties of MTX have important implications for patients being switched from oral to parenteral therapy. If a patient is a high absorber of MTX, for example, then such a switch will have a minimal effect on the response. However, patients who absorb < 50% of an oral dose may demonstrate a dramatic response when switched to parenteral therapy. For this reason, the patient described in this case was switched from oral to subcutaneous therapy.

This raises another issue related to the prescribing of MTX: namely, what is the best approach to titrating therapy? There are 2 basic approaches that can be used: the step up approach or the step down approach. In the first of these, one DMARD is administered initially, with another added if the first proves inadequate. Alternatively, treatment can be initiated with 2 or more DMARD, with individual agents discontinued after symptoms are controlled. In our initial trials with MTX in the early 1990s, the protocol started patients at 7.5 mg/week, stepped up to 12.5 mg/week at month 3, and increased to a maximum dose of 17.5 mg/week at month 6. However, the trend today is to start with higher doses and to accelerate more rapidly over the first 4 to 6 weeks of therapy. Hence, our most recent protocol was designed to start patients at 10 mg/week, increase to 17.5 mg/week at Week 6, and step up again to 22.5 mg/week at Week 12. However, we might obtain even more rapid control of erosions if we started patients on even higher doses (i.e., 20 or 25 mg) and stepped down in the case of responders. Although this approach is not currently being used, there do not appear to be any data that contraindicate it. In the recent etanercept study in patients with early RA, for example, patients started 7.5 mg of MTX and achieved their target of 20 mg/week at Week 8[4]. However, this presents the practical problem of how often a patient can be seen at a given center.

Lastly, the patient we are discussing started folic acid, an appropriate choice if toxicity is the limiting factor with MTX, a folic acid antagonist. Generally, patients start at 1 mg/day, titrating upward to 3 or 4 mg/day if necessary. The main benefit of this approach is that it makes it possible to administer higher doses of MTX and thereby enhance its efficacy. Several studies have shown that the use of folic acid not only reduces oral ulcers in patients receiving MTX, but also significantly decreases nausea and other gastrointestinal symptoms[5,6]. Folate replacement may also have a beneficial effect on cytopenias, liver toxicity, elevated homocystine levels, and other more serious toxicities. While some centers administer folic acid routinely as prophylaxis in all patients receiving MTX, I do not recommend this policy. A number of studies suggest that folate replacement does not impair the clinical efficacy of MTX, but we do not know for certain whether this is the case, particularly with regard to radiographic erosions. Nonetheless, the decision to add folic acid to the patient's MTX regimen was well considered in light of the MTX-related side effects that she was experiencing, and thus enabled her to successfully use higher doses of her MTX therapy.

Rationale for Combination Therapy. Unfortunately, few patients achieve remission on MTX monotherapy and most, as was true, of this patient, will ultimately require combination therapy (Table 1). In fact, the use of DMARD combinations to treat RA has become standard practice in most parts of the world in recent years. Whereas a metaanalysis performed as recently as 1994 failed to identify any support for combination therapy in RA, a survey of US rheumatologists conducted a mere 3 years later revealed that 99% of practitioners used combinations of DMARD to treat more than 25% of their patients with RA[7,8]. The most widely used combination in the US is MTX and hydroxychloroquine (HCQ), which is prescribed by 99% of American rheumatologists. The next most common combinations are MTX and sulfasalazine (84% of rheumatologists), and sulfasalazine and HCQ (63% of rheumatologists). Furthermore, almost 70% of rheumatologists reported using 3 or more DMARD in combination to treat a subset of patients with highly active or severe disease, an increase of almost 40% over a mere 2 years[8].

Excellent data now exist for the triple combination of MTX, HCQ and sulfasalazine in patients with early or well established disease, or in those who have had a suboptimal response to MTX alone. In addition, the combinations of MTX and cyclosporin A, or MTX and leflunomide, appear to be beneficial in some patients. The rationale for combination therapy in RA is based on 3 factors: the recognition that most

Table 1. Combination DMARD regimens.

- MTX + HCQ
- MTX + sulfasalazine
- MTX + HCQ + sulfasalazine
- Sulfasalazine + HCQ
- MTX + leflunomide
- MTX + cyclosporine A
- MTX + etanercept
- MTX + infliximab

MTX = methotrexate; HCQ = hydroxychloroquine.

DMARD lose their efficacy over time, the growing reluctance of rheumatologists to accept modest clinical improvement, and a growing body of data supporting the relative safety and enhanced efficacy of multiple DMARD therapy as compared with monotherapy[9-11].

MTX and cyclosporin A. As noted above, one of the treatment options for patients who have failed single agent MTX therapy is to add cyclosporin A to the initial MTX treatment regimen. Tugwell, *et al* published a study in which they described their experience with this combination[11]. In this 6 month double blind multicenter trial, 148 patients with severe RA who had demonstrated only a partial response to MTX (mean dose, 10.2 mg/week) were randomized to treatment with either MTX and cyclosporin (75 patients) or MTX and placebo (73 patients). The mean duration of disease was about 10 years; 85% of patients had functional Class II disease and 15% had Class III disease. The results of this study showed an advantage for combination therapy over MTX monotherapy on all outcome measures, including number of tender/swollen joints, pain, degree of disability, physician/patient global assessment of disease activity, and the erythrocyte sedimentation rate (ESR). Approximately half (48%) of the patients receiving MTX and cyclosporine improved on the ACR (American College of Rheumatology) 20, as compared with 16% of patients receiving MTX and placebo. This difference between groups was statistically significant ($p < 0.001$) in favor of MTX and cyclosporine. Nineteen (25%) patients in the MTX and cyclosporine group withdrew from the study because of 9 adverse events, while 12 (16%) patients in the MTX and placebo group withdrew because of 5 adverse events. The toxicity of combination therapy was similar to that associated with single agent therapy, but the patients receiving cyclosporine had statistically significant elevations of serum creatine.

However, the main drawback to the use of cyclosporin A, both as monotherapy and as combination therapy, is potential toxicity associated with longterm use. Yocum and colleagues reported on the longterm safety of cyclosporine, both alone and in combination with MTX, in the treatment of active RA based on an analysis of 3 US open label extension studies[12]. A total of 335 patients continued cyclosporine in these trials, 177 of whom used the drug for 4 to 6 months. After 24 weeks of open label therapy, 244 (73%) of the 335 patients who continued on cyclosporine during these extension studies were still taking the drug. This number declined to 193 patients (58%) after 48 weeks and to 75 patients (22%) at 72 weeks. Of this latter group, 21 (28%) patients were receiving cyclosporine in combination with MTX. In other words, about 25% of patients dropped out every 6 months for the first 18 months, and only 22% of patients remained on treatment after 3 years. The main reason for study discontinuation was an elevated (>30%) serum creatinine, which reversed with a reduction in dosage or discontinuation of therapy. Patients also dropped out because of hypertension and loss of efficacy. However, cyclosporine was associated with a stable therapeutic effect for up to 24 months. The side effect profile of cyclosporine was similar, independent of whether it was used as monotherapy or in combination with MTX.

Proudman and colleagues reported in a population of patients with RA with poor prognoses, that the combination of MTX, cyclosporin A and intraarticular corticosteroids did lead to more rapid disease suppression, but did not result in significantly better ACR response or remission rates than sulfasalazine monotherapy[13]. Thus, despite some reasonable success in short term, double blind studies, the longterm, followup data are not particularly encouraging for the use of MTX and cyclosporine.

MTX and leflunomide. Because leflunomide is a relative newcomer to the antirheumatic armamentarium, it has yet to be determined what the outcome might be if patients who were suboptimal responders to MTX were switched to leflunomide. However, some preliminary data suggest that leflunomide may be effective when used in combination with MTX in patients with a suboptimal response to MTX. Weinblatt, *et al* recently reported the results of a 52 week open label study, which was designed to assess the pharmacokinetics, safety, and clinical effects of leflunomide 10 to 20 mg/day when added to MTX therapy[14,15]. This combination appeared promising since these drugs possess complementary mechanisms of action. The study population was comprised of 30 patients with active RA, despite longterm (≥ 6 months) MTX therapy (mean dose, 17 mg/week). The mean duration of RA for the group was 13.6 years, and the patients had been treated with an average of 2.9 DMARD (not including MTX). The patients were required to remain on the same dose of MTX throughout the study. Twenty-three (77%) patients completed 52 weeks of treatment.

The results of this trial showed that combination therapy with MTX and leflunomide was generally well tolerated, and that there are no significant pharmacokinetic interactions between the drugs. The most notable adverse event was an elevation of serum transaminase levels in 60% of patients, which had not been observed when MTX was used alone and resulted in treatment discontinuation in 3 patients. Because of the potential risk of serious liver damage, caution should therefore be exercised when MTX and leflunomide are used in combination. Although efficacy was not the primary outcome measure in this open label study, 53% of the patients met the ACR 20 at 6 months and 57% met these criteria at 9 months. In addition, 2 patients met the ACR criteria for remission after 1 year of combination therapy.

In a double blind placebo controlled trial in patients with active RA who were not responding to MTX treatment alone, the addition of leflunomide to MTX (mean dose average 16 mg/week) provided a significant therapeutic advantage. The ACR 20 response rates at 24 weeks were 46.2% for leflunomide and MTX versus 19.5% for placebo and MTX[16]. These findings suggest that the combination of MTX and lefluno-

mide might prove useful for the treatment of RA, although further information on liver enzyme elevations and more longterm experience with leflunomide, both alone and in combination with MTX is needed.

Triple drug combinations. Another option for our patient is to initiate triple DMARD therapy. One of the first studies to evaluate the use of this approach in the treatment of RA was a longterm trial in patients with RA who had failed on at least one DMARD[17]. The Paulus 50 was used instead of the Paulus 20 to assess improvement and the goal of treatment was remission. Patients were randomized to one of 3 treatment groups: MTX alone, sulfasalazine and HCQ, or triple drug therapy. The average duration of disease of patients in the MTX and triple therapy groups was more than 9 years and about 50% of the study participants were receiving low dose prednisone at the time of enrollment.

As shown in Figure 1, there was a significant advantage for triple drug therapy as compared with MTX monotherapy (or, for that matter, sulfasalazine and HCQ) from Month 9 through 24 with respect to time until treatment failure (i.e., efficacy or toxicity). Specifically, 33% of patients receiving MTX alone achieved a Paulus of 50 at the end of 2 years of double blind treatment, as compared with almost 80% of patients receiving triple therapy. When patients who had failed to achieve the 50% improvement criteria and who had not received triple drug therapy during the initial double blind portion of the study were treated with sulfasalazine and HCQ, in addition to MTX (median dose, 17.5 mg/week), significant improvement was observed according to various measures of efficacy[10,17]. These included morning stiffness, swollen/tender joint score, ESR, and both the patients' and the physicians' global assessment of improvement. These findings indicate that the suboptimal response so often associated with MTX monotherapy need not necessarily imply clinical failure.

In a subsequent 2 year, double blind randomized trial (the Triple II study) we sought to determine whether triple drug therapy offered an advantage over combination therapy with MTX and sulfasalazine or MTX and HCQ in 171 patients with RA of greater than 6 months' duration (unpublished observation). The patients participating in this study received 2 mg/day of sulfasalazine, whereas those enrolled in the previous study received 1 mg/day. The dose of MTX was escalated to 17.5 mg/day, while the dose of HCQ remained stable at 400 mg/day. The protocol was such that patients who discontinued treatment for any reason, be it side effects or protocol violations, were defined as treatment failures. To be enrolled, patients could be MTX naïve or could have failed MTX at the dose used in this study (17.5 mg). These patients were then randomized equally into the 3 treatment groups. The primary endpoint of the study was the ACR 20.

At the end of 2 years of treatment, patients in the triple drug group had achieved an ACR 20 more often than those in the MTX plus HCQ or MTX plus SSA groups.

CASE 2: MTX FAILURE

A 53 year old man with established RA has taken prednisone 7.5 mg/day, MTX 25 mg/wk SQ, and HCQ 400 mg/day for 6 months. He meets the ACR 50, but continues to have 6 swollen joints and 8 tender joints. What treatment strategy should be used?

Additional options for patients with refractory RA. There are various options for patients with refractory RA, like the patient described here, including switching to any of the treatment combinations described above. For example, Figure 2

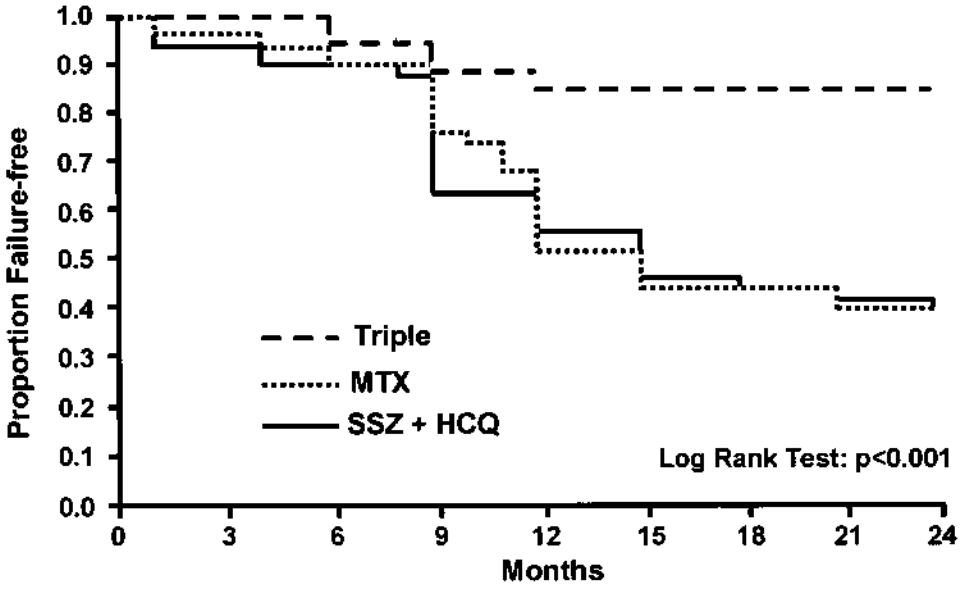

Figure 1. Patients with good responses to study treatment. (with permission O'Dell J, et al. N Engl J Med 1996;334:1287-91. Copyright © 2001 Massachusetts Medical Society. All rights reserved.).

summarizes the clinical outcome in patients who had failed taking MTX (mean dose, 12.5-17.5 mg/wk) and were switched to alternative DMARD regimens[18,19]. About 46% of those receiving leflunomide, and 48% of those receiving cyclosporine plus MTX[15,11].

Given the association between thyroid disease and RA, it is always important to check a patient's TSH (thyroid stimulating hormone) level before considering a change in treatments. A lack of clinical response or exacerbation of the disease may be precipitated by a change in thyroid status.

In addition, there is a growing body of evidence suggesting that the use of minocycline may be beneficial in the treatment of RA[20]. Specifically, the results of 2 double blind randomized placebo controlled trials have shown that the addition of the tetracycline derivative, minocycline, to existing therapies results in significant improvement in clinical variables in patients with advanced disease[21,22]. Some data also suggest that tetracyclines may exert antiarthritic, as well as antibacterial, effects[23,24].

An alternative approach in cases of refractory RA is to use conventional DMARD in combination with an immunosuppressive agent, such as azathioprine. The results of an open label study by McCarty, *et al*, which presented one rheumatologist's experience with the use of multiple remittive agents in 169 patients with seropositive RA seen from 1974 to 92 (using whatever it took to suppress joint inflammation), showed that combination therapy generally produced significant improvement according to every outcome measure[25]. These included morning stiffness, grips, PIP (proximal interphalangeal) circumference, articular index, ARA functional class, ESR, CRP (c-reactive protein), and platelets. The authors stressed the importance of continuing therapy for at least 1 year.

Lastly, agents that block tumor necrosis factor, such as etanercept and infliximab, have successfully been used to treat patients who resist MTX[26-29]. Although the exact role of these and other biological response modifiers as components of (or alternatives to) MTX combinations remains to be determined, it is possible that these new agents will demonstrate additive or synergistic efficacy when used with standard DMARD regimens, thereby further enhancing our treatment options for patients with RA. Studies that compare biological agents head-to-head with conventional DMARD options are a critical need.

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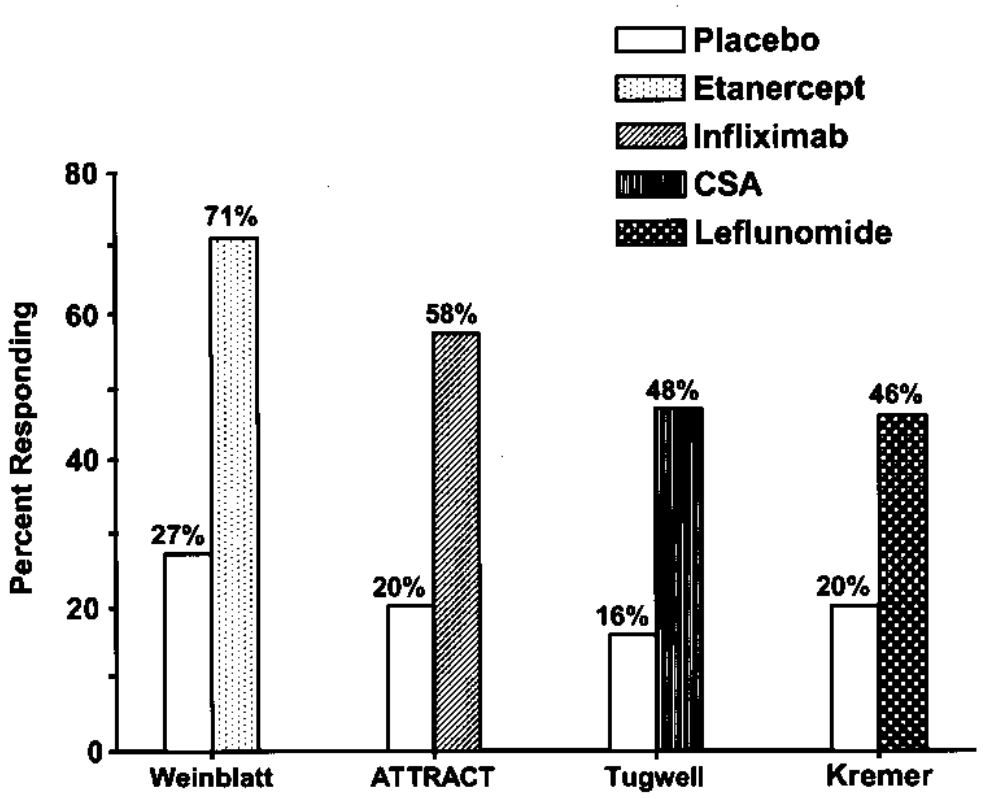

Figure 2. Percentage of patients achieving ACR 20 after failing to respond to MTX therapy[11,15,16,19].

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