Efficacy and Safety of Methotrexate in Combination with Other Non-biologic Disease-modifying Antirheumatic Drugs (DMARDs) in Treatment of Rheumatoid Arthritis

Isabel Castrejón, M.D., Kathryn A. Gibson, M.D., Ph.D., and Theodore Pincus, M.D.

Abstract
Methotrexate (MTX) is well-established as the “anchor drug” for patients with rheumatoid arthritis (RA), to be used early and aggressively, with higher long-term effectiveness, tolerability, and safety than any other disease-modifying antirheumatic drug (DMARD). However, about 20% to 40% of patients experience incomplete responses to MTX and require further therapy, with options including other non-biologic DMARDs, low dose glucocorticoids, and biologic agents. Non-biologic DMARDs in combination with MTX may provide similar efficacy to a biologic agent in clinical trials, with fewer adverse events and lower costs. This review presents a summary of 21 clinical trials documenting the efficacy and safety of MTX in combination with other non-biologic DMARDs.

Methods
A PubMed search was performed to search for studies that included at least one arm of treatment involving MTX in combination with other non-biologic DMARDs. We used the following search terms: rheumatoid arthritis, randomized trial, MTX, DMARDs, triple therapy rheumatoid, and combination therapy to retrieve clinical trials, including combination therapy of MTX with other DMARDs. We also performed a hand search of references from the included reports. The search yielded 21 clinical trials, but the review was not exhaustive. It was not possible to pool these trials because of different interventions and primary outcomes. Therefore, a brief summary of each trial is presented, including description of participants, duration of the study, intervention, primary outcome, and results.

Results
An overview of the inclusion criteria, different treatments used, primary and secondary outcomes, and quality of the trials using the Jadad scale is presented in Table 1. The Jadad scale evaluates the methodological quality of a clinical trial on a scale of 0 to 5 (yes = 1, No = 0). One point each may be given if the study was randomized, double blind, and
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<th>Study</th>
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<th>Outcomes</th>
<th>Quality*</th>
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| Tugwell 1995<sup>9</sup> | N = 148 participants meeting the 1988 ACR criteria<sup>a</sup>, ≥ 6 SJC | • MTX+Placebo (75)  
• MTX+Cyclosporine (73) | Primary: tender joint counts  
Secondary: patients and physician’s global assessment, pain, function | Jadad 5 |
| Proudnan 2000<sup>11</sup> | N = 82 participants meeting the 1988 ACR criteria<sup>a</sup> with no previous treatments poor prognosis, disease duration < 12m | • SSZ (42)  
• MTX+Cyclosporine+ methylprednisolone injections (40) | Primary: clinical improvement by ACR criteria 40, remission and ACR20/50  
Secondary: DAS28 and radiological damage by modified Sharp/Van der Heijde | Jadad 2 |
| Marchesoni 2003<sup>12</sup> | N = 61 RA patients with active disease (> 6 SJC and > 8 TJC) | • MTX+Placebo (31)  
• MTX+Cyclosporine (30) | Primary: radiographic damage by modified Sharp/Van der Heijde  
Secondary: clinical and laboratory parameters | Jadad 3 |
| Gerards 2003<sup>13</sup> | N = 508 participants meeting the 1987 ACR criteria<sup>a</sup>, disease duration < 3 years, > 6 TJC or SJC | • Cyclosporine+Placebo (60)  
• Cyclosporine+MTX (60) | Primary: ACR remission<sup>37</sup> and radiographic damage by Larsen score  
Secondary: single items, HAQ, ACR20/50/70 | Jadad 5 |
| Hetland 2008<sup>14</sup> | N = 160 participants meeting the 1988 ACR criteria<sup>a</sup> with a disease duration < 6m and > 2 SJC | • MTX+Placebo (80)  
• MTX+Cyclosporine (80) | Primary: ACR20 response at 2 years  
Secondary: remission, cumulative dose of betamethasone, and radiographic progression | Jadad 5 |
| Choy 2007<sup>15</sup> | N = 467 participants with early RA, with a disease duration < 24m and ≥ 3 SJC and ≥ 3 TJC | • MTX (117)  
• MTX+Cyclosporine (119)  
• MTX+prednisolone (115)  
• MTX+Cyclosporine+prednisolone (116) | Primary: development of new erosions in x-rays of hands and feet  
Secondary: changes in total Larsen x-ray score, function (HAQ), quality of life (SF-36), disease activity (DAS28 and ACR20/50/70) and adverse events | Jadad 5 |

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### Table 1 Continued

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| Möttönen 1999<sup>21</sup> | N = 199 participants meeting the 1988 ACR criteria, ≤ 2 yrs disease duration, > 5 SJC, > 10 TJC | • MTX+SSZ+HCQ+Prednisolone (58)                  | **Primary:** ACR remission<sup>27</sup>  
**Secondary:** ACR50, improvement in single items, radiographic damage, and side effects | Jadad 3   |
| FIN-RACo trial          |                                                                               | • DMARD in monotherapy                            |                                               | Not blinded |
| Çağluğeri 1999<sup>22</sup> | N = 180 participants meeting the ACR criteria, with > 6 TJC or > 3 SJC, ≤ 1 year and DAS > 3.0 | • MTX or SSZ or HCQ (60)                          | **Primary:** ACR remission criteria<sup>27</sup>  
**Secondary:** morning stiffness, NSAIDs requirement, Ritchie articular index   | Jadad 1   |
| Dougados 1999<sup>23</sup> | N = 209 participants meeting the 1988 ACR criteria, ≥ 6 SJC, ≥ 9 TJC, previous NSAIDs and disease duration > 1 year and DAS > 3.0 | • SSZ (68)                                       | **Primary:** ACR20  
**Secondary:** ACR50/70, individual components of the ACR response, toxicity | Jadad 4   |
| O’Dell 2002<sup>24</sup>   | N = 171 participants meeting the 1988 ACR criteria, > 6 SJC, > 9 TJC, previous NSAIDs and disease duration > 1 year and DAS > 3.0 | • MTX+HCQ (58)                                   | **Primary:** ACR20  
**Secondary:** ACR50/70, individual components of the ACR response, toxicity | Jadad 5   |
| Methotrexate in combination with leflunomide | N = 263 participants meeting the 1988 ACR criteria, ≥ 6 SJC, ≥ 9 TJC | • MTX+Leflunomida (130)                           | **Primary:** ACR20  
**Secondary:** ACR50/70, individual components of the ACR response, toxicity | Jadad 5   |
| Lehman 2005<sup>29</sup> | N = 65 participants meeting the 1987 ACR criteria, ≥ 6 SJC, ≥ 5 TJC, previous NSAIDs and disease duration ≤ 10 years and DAS < 4.3 | • MTX+placebo (27)                               | **Primary:** ACR20  
**Secondary:** ACR50/70, response to individual criteria | Jadad 5   |
| Triple therapy versus methotrexate in combination with an anti-TNF | N = 508 participants meeting the 1987 ACR criteria, ≥ 6 SJC and TJC | • Sequential monotherapy (122)  
• Step-up combination MTX+SSZ+HCQ (115)  
• Initial combination MTX+SSZ+Prednisone (133)  
• Initial combination MTX+Infliximab (126) | **Primary:** functional ability by HAQ and radiographic damage by modified Sharp/Van der Heijde  
**Secondary:** ACR20/50/70 and clinical remission defined as DAS < 1.641 | Jadad 3   |

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<tr>
<td>Van Vollenhoven 2009</td>
<td>N = 487 participants meeting the 1987 ACR criteria, DAS28 ≥ 3.2, disease duration &lt; 1 yrs, no previous treatment</td>
<td>• MTX+SSZ+HCQ (130) • MTX+Infliximab (128)</td>
<td>Primary: number of patients achieving a good EULAR response: DAS28 decrease at least 1.2 resulting in a DAS28 ≤ 3.236 Secondary: moderate EULAR response, ACR20/50/70</td>
<td>Jadad 3 Not blinded</td>
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<td>Swefot trial</td>
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<td>Moreland 2012</td>
<td>N = 755 participants meeting the 1987 ACR criteria, &gt; 4 TJC or SJC, disease duration &lt; 3yrs</td>
<td>• Immediate MTX+Etanercept (244) • Immediate MTX+SSZ+HCQ (132) • Step-up from MTX to MTX+Etanercept (255) • Step-up from MTX to MTX+SSZ+HCQ (124)</td>
<td>Primary: change in the DAS28 between week 48 and 102 Secondary: radiographic progression, ACR20/50/70, modified-HAQ</td>
<td>Jadad 5</td>
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<td>O’Dell 2013</td>
<td>N = 353 participants meeting the 1987 ACR revised criteria, MTX at stable dose (15-25 mg) for 12 weeks and DAS28 ≥ 4.4</td>
<td>• MTX+SSZ+HCQ (178) • MTX+Etanercept (175)</td>
<td>Primary: change in the DAS28 at 48wk Improvement = decrease ≥ 1.2 Secondary: radiographic progression, % of participants with DAS28 ≤ 3.2, ACR20/50/70, CDAI, HAQ</td>
<td>Jadad 5</td>
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<td>Leirisalo-Repo 2013</td>
<td>N = 99 participants meeting the 1987 revised ACR criteria, disease duration &lt; 12m and DMARDs naïve, &gt; 6 SJC and TJC</td>
<td>• MTX+SSZ+HCQ+Prednisolone+ Placebo (49) • MTX+SSZ+HCQ+Prednisolone+ Infliximab (50)</td>
<td>Primary: remission by the modified ACR criteria and radiological changes at 24m Secondary: number of patients with sustained remission, DAS28, ACR20/50/70</td>
<td>Jadad 5</td>
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*Quality was assessed according to the Jadad scale. RCT, randomized control trial; ACR, American College of Rheumatology; MTX, Methotrexate; SSZ, sulfasalazine; HCQ, hydroxychloroquine; DAS28, Disease Activity Score for 28-joint counts; CDAI, Clinical Disease Activity Index; HAQ, Health Assessment Questionnaire; TJC, tender joint count; SJC, swollen joint count; ESR, erythrocyte sedimentation rate.
a description of withdrawals and dropouts was included. Two additional points may be given if the method of randomization was appropriate and described, and the method of blinding was appropriate and described. Patients met American College of Rheumatology (ACR) classification criteria for RA,\(^8\) had active disease according to different criteria, and age greater than 18 years. The follow-up ranged from 24 weeks to 2 years. The quality of the included studies generally was high.

**Methotrexate in Combination with Cyclosporine**

Six trials compared MTX in combination with cyclosporine. The study of Tugwell and coworkers\(^9\) was reported in 1995, involving patients with severe RA and incomplete responses to MTX. This design was the prototype “step-up” clinical trial—adding another therapy to MTX monotherapy in patients who had experienced incomplete responses to MTX.\(^10\) The step-up design has been used in many subsequent trials, including many early trials of biological agents added to MTX in incomplete responders to MTX monotherapy. In the Tugwell study, the primary outcome of tender joint count was improved significantly more in the combination of cyclosporine and MTX than MTX monotherapy over 6 months. Adverse events were not substantially increased compared to monotherapy with each medication.\(^9\)

Proudman and colleagues\(^11\) compared sulfasalazine (SSZ) monotherapy with a combination that included MTX, cyclosporine, and methylprednisolone. Both groups had significant improvement in all ACR core data set measures and ACR20, with greater improvement in the combination group, which, however, was not statistically significant. More withdrawals due to lack of efficacy were seen in the SSZ monotherapy group than in the combination group, which was statistically significant. The investigators suggested that their data supported step-up from monotherapy in new patients rather than combination therapy as the initial treatment.

In 2003, Marchesoni and associates\(^12\) extended evidence of the value of combination cyclosporine and MTX, with a longer follow-up of 12 months in patients with early RA and primary outcome of radiographic damage. Patients in the combination group had three times lower radiographic progression than patients who were treated with monotherapy. The rates of ACR20, 50, and 70 responders did not differ significantly, possibly because of low doses of therapies and low sample size.

Also in 2003, Gerards and coworkers\(^13\) compared the combination of cyclosporine plus MTX with cyclosporine plus placebo, again with a primary outcome of radiographic progression. The combination was found to have greater efficacy compared to cyclosporine in monotherapy. There was a trend toward greater clinical improvement in the combination therapy group, which, however, was not statistically significant. The percentage of patients achieving remission was similar and low in both groups.

Hetland and associates reported CIMESTRA (Cyclosporine, Methotrexate, Steroid in RA)\(^14\) to compare MTX monotherapy to MTX plus cyclosporine. A higher level of ACR20 and ACR50 responses was seen in patients randomized to MTX plus cyclosporine than to MTX monotherapy. However, the combination did not have any additional effect on remission rate and radiographic outcome, likely explained by intensive therapy with intraarticular betamethasone injections in patients in both groups. The effects of the intraarticular injections may have obscured possible differences between MTX monotherapy and MTX plus cyclosporine (see article on strategy trials in this supplement).

Choy and colleagues\(^15\) reported the CARDERA (Combination Antiinflammatory Drugs in Early Rheumatoid Arthritis) trial, which included four arms: MTX monotherapy; MTX plus cyclosporine; MTX plus step-down prednisolone; and MTX plus cyclosporine plus prednisolone. The primary outcome of new erosions was lowest in the triple therapy group and differed significantly in the prednisolone and cyclosporine group compared to the MTX monotherapy group. HAQ scores were decreased in all four groups but most in the combination therapy group. Adverse events did not differ significantly in the groups.

Cyclosporine can be an efficacious treatment for RA but cannot be given over long periods because of elevations in blood pressure and serum creatinine.\(^16\) A primary use at this time is to treat flares over limited periods of a few months.

**Methotrexate in Combination with Sulfasalazine, Hydroxychloroquine or Prednisolone**

Seven studies have documented the effectiveness of combinations of MTX with SSZ, hydroxychloroquine (HCQ), and prednisolone.

The first demonstration of the efficacy of “triple therapy”\(^17\) of MTX, SSZ, and HCQ was reported by O’Dell and coworkers in 1996.\(^17\) The primary outcome was “50% improvement.” Superior efficacy was found for the triple combination over MTX monotherapy or SSZ in combination with HCQ.

Haagsma and colleagues\(^18\) reported a modest trend favoring combination of SSZ+MTX versus MTX or SSZ as monotherapy. However, these differences in the primary outcome—a change in the disease activity score (DAS)—were not statistically significant, possibly as only 69 patients were enrolled.

The COBRA trial\(^19\) compared the combination of MTX with SSZ and prednisolone versus SSZ monotherapy. A higher percentage of patients improved by clinical measures in the combined treatment group, and radiological damage was increased significantly more in the SSZ monotherapy group (4 versus 12 units on the modified Sharp/van der
Heijde at 80 weeks). Significantly fewer patients stopped combined treatment than stopped SSZ. In a subsequent study reported in 2002, Landewe and associates found that initial intensive treatment induced a sustained reduction in the rate of long-term radiologic progression.

The FinRACO trial randomized patients to triple therapy plus prednisolone versus a SSZ monotherapy that was changed to MTX if SSZ did not achieve a response greater than 25%. The primary outcome was remission according to ACR criteria. Patients in the triple therapy group were significantly more likely to achieve remission than DMARD monotherapy.

Çalgüneri and coworkers randomized patients to receive single, double, or triple therapy with MTX, SSZ, and HCQ; again with ACR remission criteria as the primary outcome. Triple therapy was superior to double therapy, which was superior to single therapy.

Dougados and colleagues compared MTX to SSZ to a combination of both medications as “double therapy” in 205 RA patients over 1 year. Combination therapy had greater efficacy in reducing the Ritchie Articular Index and DAS, which was statistically significant. Trends favoring the combination were seen for some other measures, but none was statistically significant. The investigators pointed out that 6 months may be sufficient to document differences between combinations of two active treatments may require a longer period; further, triple therapy has greater efficacy in reducing the Ritchie Articular Index and particular steroid treatment was significantly smaller in the combination group. The predominant adverse events were mucocutaneous reactions. Although adverse events were more common with gold, no serious adverse events were seen. Moreover, more patients in the MTX monotherapy group discontinued treatment because of a lack of efficacy. The investigators concluded that the combination of MTX plus intramuscular gold can be effective, especially when cost of a biological agent is an issue.

In 2005, Lehman and coworkers reported a clinical trial to compare MTX in combination with injectable gold salts to MTX monotherapy in MTX incomplete responders. The primary outcome was ACR20. The combination of MTX plus intramuscular gold was significantly more effective than MTX monotherapy in increasing the percentage of ACR20 responders, and the proportion of patients needing intraarticular steroid treatment was significantly smaller in the combination group. The predominant adverse events were mucocutaneous reactions. Although adverse events were more common with gold, no serious adverse events were seen. Moreover, more patients in the MTX monotherapy group discontinued treatment because of a lack of efficacy. The investigators concluded that the combination of MTX plus intramuscular gold can be effective, especially when cost of a biological agent is an issue.

**Methotrexate in Combination with Injectable Gold Salts**

Injectable gold salts were once the most widely used DMARD for the treatment of RA. However, this therapy is used in few patients at this time, because MTX, SSZ, and even HCQ have fewer adverse events and greater long-term effectiveness. Some observational studies suggested that the combination of MTX and gold salts is effective and well tolerated with no serious side effects.

In 2005, Lehman and coworkers reported a clinical trial to compare MTX in combination with injectable gold salts to MTX monotherapy in MTX incomplete responders. The primary outcome was ACR20. The combination of MTX plus intramuscular gold was significantly more effective than MTX monotherapy in increasing the percentage of ACR20 responders, and the proportion of patients needing intraarticular steroid treatment was significantly smaller in the combination group. The predominant adverse events were mucocutaneous reactions. Although adverse events were more common with gold, no serious adverse events were seen. Moreover, more patients in the MTX monotherapy group discontinued treatment because of a lack of efficacy. The investigators concluded that the combination of MTX plus intramuscular gold can be effective, especially when cost of a biological agent is an issue.

**Triple Therapy (Methotrexate Plus Sulfasalazine Plus Hydroxychloroquine) Compared to Methotrexate in Combination with an Anti-tumor Necrosis Factor (anti-TNF) Biological Agent**

The primary options for patients who have experienced an incomplete response to MTX are the addition of another conventional DMARD or of a biological agent. Five clinical trials included randomization to groups designed to compare these two strategies. The BeSt trial included four different treatment arms, one of which involved initial combination of MTX, SSZ, and prednisone (COBRA strategy) and another initial combination of MTX with infliximab. One trial compared the addition of infliximab with the addition of SSZ and HCQ to MTX, two compared triple therapy to the combination of MTX plus etanercept, and another trial compared triple therapy in combination with prednisolone to MTX plus infliximab.

In the BeSt trial (Dutch acronym for Behandel-Strategieen, “treatment strategies”), combination therapy including either MTX, SSZ, and prednisone or MTX and infliximab resulted in earlier functional improvement compared with sequential monotherapy or step-up combinations. However, after 1 year, similar marked improve-
ment was seen in all groups for the primary outcome of HAQ functional capacity, possibly explained by close monitoring of patients with protocol-driven escalation of therapy. Radiographic progression was lower in both initial combination therapy groups, although differences were very small compared to the other groups. It is not yet known whether rapid relief of symptoms and improvement achieved with the initial combination therapy may result in better long-term outcomes.

The Swefot trial compared triple therapy with MTX plus SSZ plus HCQ with the combination of MTX plus infliximab. The primary outcome involved the number of patients with a good EULAR response and a DAS 28 decrease of at least 1.2 units resulting in a DAS 28 ≤ 3.2. No significant differences were seen after 6 months, but an advantage was seen to MTX plus infliximab at 12 months. The investigators concluded that although the combined regimen with an anti-TNF was superior in groups, specific factors in individual patients could lead to consideration of triple therapy without anti-TNF.

The TEAR trial involved patients with early RA and included a subgroup of patients who experienced an incomplete response to MTX and were randomized to the addition of etanercept or SSZ and HCQ to their MTX monotherapy. The primary outcome was change in DAS28 between week 48 and week 102. No differences were seen between the two groups, with similar 2-year improvements in functional status and relatively little difference in radiographic progression, again likely explained by protocol-driven escalation of therapy.

In a recent study, O’Dell and associates compared triple therapy of MTX plus SSZ plus HCQ to MTX plus etanercept in patients who had incomplete responses to MTX at stable doses of 15 to 25 mg weekly for at least 12 weeks. The primary outcome was change in DAS28 at 48 weeks. Both groups showed significant improvement over the first 24 weeks; DAS28 responses favored MTX plus etanercept at 24 weeks, but no significant differences were seen compared to triple therapy at 48 weeks. No significant differences were seen between the two groups in radiographic progression or physical function. At 24 weeks, the trial design allowed switching to the other arm if DAS28 was not decreased by more than 1.2 units. Switching to the alternative therapy occurred with equal frequency in the two groups. No significant differences were seen between the two groups in ACR20 and 50 responses at either 24 or 48 weeks. The frequencies of adverse events were similar in the two groups, although gastrointestinal disorders occurred more frequently with triple therapy and infections more with MTX plus etanercept.

The NEO-RACo trial compared the “FIN-RACo” regimen of triple therapy in combination with infliximab versus the FIN-RACo regimen in combination with placebo in patients who had no previous treatment with DMARDs. The primary outcome was remission by the modified ACR criteria. At 24 months, no differences were seen in the percentage of patients in remission, but more patients were in sustained remission and there was lesser radiological progression in the infliximab group.

**Discussion**

Methotrexate remains the “anchor drug” and the first choice for treatment of RA by most rheumatologists. However, many patients experience incomplete responses to MTX monotherapy, and it is necessary to add additional therapy. Two major options include addition of a non-biologic DMARD to MTX or a biologic agent. Triple therapy, i.e., the combination of MTX plus SSZ plus HCQ, appears an efficacious and safe therapy toward favorable long-term outcomes.

It has been documented that triple therapy is superior to each of these DMARDs in monotherapy or even in double combination. Moreover, it appears that triple therapy may provide similar efficacy to a combination of MTX and a biologic agent in many patients while reducing the cost of therapy considerably. In a trial that compared MTX plus etanercept to triple therapy in which patients and physicians could switch therapies if preferred, observed rates of switching were nearly identical, further validating the similarity of the regimens. By contrast, in the Swefot trial, although no differences between MTX plus infliximab and triple therapy were seen at 6 months, MTX plus infliximab appeared superior at 12 months. Moreover, in the most recent O’Dell study, a more rapid response was seen in the MTX plus etanercept group compared to the triple therapy group, but it is not known whether a more rapid response translates into a longer-term benefit.

The combination of MTX with cyclosporine improves clinical parameters and reduces radiographic progression. However, renal toxicity and episodes of hypertension, which require close monitoring, limit its use to intermittent therapy for flares in patients with RA. One study has shown the beneficial effect of combining MTX with gold. MTX plus leflunomide may be efficacious, although close monitoring of hepatic function is required.

In conclusion, patients with RA who fail to achieve adequate disease control or remission with MTX monotherapy may benefit from the addition of another non-biologic DMARD with significant clinical improvement and good tolerability. Some experts suggest initial triple therapy rather than MTX monotherapy, as an alternative to the combination of MTX with a biological agent. Several combinations are available to provide efficacious and safe options. Aggressive therapy adjusted to a “treat to target” goal should be initiated in all RA patients, based on a shared decision between doctors and patients.

**Disclosure Statement**

None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but
not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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