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# Drug combinations with methotrexate to treat rheumatoid arthritis

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## ABSTRACT

*MTX is still considered the anchor drug among the disease-modifying antirheumatic agents, and it is widely accepted as first line treatment in the management of rheumatoid arthritis (RA). The ultimate therapeutic goal in treatment of RA is remission or at least low disease activity and this goal may not always be achieved with MTX monotherapy. Over the last two decades drug combinations based on MTX have been used increasingly to treat patients with RA. Combination DMARD therapy may be used initially or in a step-up strategy after MTX monotherapy in patients with persistently active disease on monotherapy. Many different MTX based combination regimens have been studied. Frequently used combinations on an MTX background include leflunomide, cyclosporine, azathioprine, sulfasalazine, gold and hydroxychloroquine. In conclusion, the use of MTX in combination with other DMARDs may still represent a valuable therapeutic option in patients who fail to DMARD monotherapy or in whom combination therapy is considered initially. However, in patients at risk for rapid radiographic progression, the early use of biologics has to be considered.*

At present, MTX is still considered the anchor drug among the disease-modifying antirheumatic agents (DMARDs), and it is widely accepted as first line treatment in the management of RA (1-3). However, the efficacy of MTX to improve signs and symptoms of disease and to inhibit the development of structural damage varies among individual patients (4). The ultimate therapeutic goal in treatment of RA is remission or at least low disease activity and this goal is not achieved in all patients with MTX monotherapy (5).

Combining drugs with a different mode of action is a well established therapeutic

principle when treating patients with hypertension, tuberculosis and malignant disorders with the idea to achieve additional benefit without increase in toxicity compared to the same agents used sequentially (6). The earliest studies of combination therapy showed only a modest advantage but higher toxicity (7, 8). However combinations containing gold or penicillamine had lesser efficacy and greater toxicity than agents widely used at this time such as methotrexate and sulfasalazine (7).

Over the last two decades drug combinations based on MTX have been used increasingly to treat rheumatoid arthritis (9). Combination DMARD therapy may be used initially or in a step-up strategy after MTX monotherapy in patients with persistently active disease on monotherapy (10).

A Cochrane Review of 19 trials (including 2025 patients) in RA was recently published and evaluated MTX monotherapy versus its use in DMARD combination therapy (11, 12). In this meta-analysis, DMARD naive patients and patients with an inadequate response to previous MTX or other DMARDs were analysed separately. Trials in DMARD naive patients did not show a significant advantage of MTX in combination versus MTX monotherapy; withdrawals due to lack of efficacy or toxicity were similar in both groups (11-13).

Trials in MTX inadequate responder patients also did not show a difference in withdrawal rates comparing MTX combination versus monotherapy. Significant reduction of pain and improvement in physical function (measured by Health Assessment Questionnaire (HAQ)) were found in the MTX combination group, but limited to MTX-inadequate responders (11, 12). The authors of the meta-analysis concluded that trials are needed to compare MTX monotherapy in adequate doses to MTX-containing combination therapies.

Competing interests: none declared.

These questions are particularly important as reimbursement for biologic agents in most countries requires failure to prior use of MTX and most often MTX combination therapy.

Many different MTX based combination regimens have been studied. Frequently used combinations with an MTX background include leflunomide, cyclosporine, azathioprine, sulfasalazine, gold and hydroxychloroquine.

### **MTX and leflunomide**

Leflunomide (LEF) inhibits pyrimidine synthesis pathways. Although both MTX and leflunomide are potentially hepatotoxic and may suppress haematopoiesis, the rationale for combined therapy is based upon their different mechanisms of action. Kremer *et al.* investigated the potential efficacy of this combination and used a step-up strategy in MTX inadequate responders in a double-blind randomised controlled trial with patients receiving leflunomide versus placebo while continuing MTX (14).

Patients received stable dosages of MTX (15 to 20 mg/week if tolerated) and were randomly assigned to receive leflunomide (100 mg/d for 2 days followed by 10 mg/d) or matching placebo. If active disease was still present at week 8 or thereafter, leflunomide was increased to 20 mg daily. The primary outcome was defined as the proportion of patients achieving an ACR20 after 24 weeks of therapy and was significantly higher in the group receiving leflunomide plus MTX (46.2 vs. 19.5%). The rate of discontinuation and the incidence of adverse events, which were predominantly mild or moderate, were similar in both groups. Diarrhoea and elevation of serum aminotransferases were the only adverse effects seen significantly more often with LEF plus MTX than with MTX alone.

Additional support for the efficacy of leflunomide and MTX in combination was provided by the open-label extension of this trial and other smaller studies (15-17).

### **MTX and cyclosporine A**

Cyclosporine A (CsA) is an effective immunosuppressant and has complex

effects on T-cell function, including inhibition of interleukin-2 release and subsequent activation of T cells (18). Various studies have provided evidence that CsA can control symptoms and inhibit progression of joint damage in patients with active RA (19-22).

The CARDERA (Combination Anti-Rheumatic Drugs in Early Rheumatoid Arthritis) trial, a randomised controlled trial comparing MTX and placebo to MTX with prednisolone, cyclosporine or both, showed a significant reduction in development of new erosions by adding either cyclosporine or prednisolone to MTX monotherapy (23). The lowest number of new erosions was seen with the combination of the three drugs.

Additional support was provided by Marchesoni *et al.* demonstrating that in patients with early RA, CsA + MTX combination therapy led to a significantly lower rate of radiographic progression after 12 months, was effective in suppressing inflammatory articular symptoms, and was well tolerated (24).

In patients with severe rheumatoid arthritis and only partial responses to MTX, a six-month randomised placebo-controlled trial evaluated the combination of MTX with CSA in 148 patients; the patients were assigned to receive MTX (at the maximal tolerated dose) plus CSA (2.5 to 5 mg/kg per day) or placebo (25). After six months of treatment, the combination of MTX and CSA resulted in a greater reduction in the tender-joint count, the primary outcome, compared with MTX plus placebo (-7.5 vs. -2.7 joints). An ACR20 response was achieved more often in the combination group (48 vs. 16%). The clinical improvement previously observed in patients treated with the CSA + MTX combination for 24 weeks was maintained for 24 subsequent weeks, without serious adverse effects, and was also observed in the patients whose treatment was switched from placebo + MTX to CSA + MTX (26).

### **MTX and azathioprine**

In a double-blind, prospective, multicenter, controlled trial 209 patients with active RA were treated with escalating doses of MTX (5-15 mg/week),

azathioprine (AZA) (50-150 mg/day), or the combination of both (5mg MTX/week plus 50 mg AZA/day-7.5 mg MTX/week plus 100 mg AZA/day), with the option to increase the dosage at 6-week intervals, until achieving the effective dosage (AZA 150 mg/day and MTX 15 mg/week) (27).

Lower dosages of both AZA and MTX were used in the combination group. The patients were evaluated for significant clinical and laboratory improvement and assessed for radiologic progression at 48 weeks. Only 110 from 209 patients finished the study. In this study MTX monotherapy was more effective than AZA but did not show a difference to the combination of MTX. A trend towards decreased radiographic progression was noted in the MTX monotherapy patients.

Another study by Blanco *et al.* reported on acute febrile toxic reactions in patients with refractory rheumatoid arthritis who were receiving combined therapy with MTX and azathioprine (28).

### **MTX and gold**

The addition of intramuscular gold to MTX may benefit some patients who are unable to benefit from other DMARDs. In the METGO trial, 65 patients with RA and a partial response to MTX (mean dose of 18.5 mg/week) were randomly assigned to intramuscular gold (up to 50 mg per week) or placebo injections for 48 weeks while continuing MTX (29). Patients who received intramuscular gold were significantly more likely to achieve the primary outcome, an ACR20 response at week 48 (61 vs. 30%). ACR50 and ACR70 were also achieved more often with gold plus MTX versus MTX alone (26 vs. 4% and 21 vs. 0%, respectively). Intramuscular gold-related adverse events led to discontinuation of therapy in 11% of patients receiving the combination.

### **MTX and sulfasalazine**

MTX and SSZ are frequently used DMARDs in the treatment of RA, especially during the early disease course. In the double-blind placebo-controlled MASCOT study, combination therapy with sulfasalazine and MTX proved

**Table I.** Characteristic of pivotal trials on DMARD combination therapies including MTX.

| Authors / Study                  | Sample size | Study duration (months) | Strategy (trial design) | Duration       | MTX mean dose (mg/week) | DMARDs tested                   | Outcome  |
|----------------------------------|-------------|-------------------------|-------------------------|----------------|-------------------------|---------------------------------|--|
| Tugwell, 1995 (25)               | 148         | 6                       | MTX-IR (step-up)        | Established RA | 15                      | MTX vs. MTX+CSA                 | MTX+CSA > MTX (ACR20)  |
| Wilkens, 1995 (27)               | 209         | 6                       | Non-MTX-IR              | Established RA | 5–15                    | AZA vs. MTX vs. MTX+AZA         | MTX+AZA = MTX and MTX > AZA (DAS44)  |
| O'Dell, 1996 (33)                | 102         | 6                       | Non-MTX-IR (parallel)   | Established RA | Up to 17.5              | MTX vs. SSZ+HCQ vs. MTX+SSZ+HCQ | MTX+SSZ+HCQ > SSZ+HCQ and MTX+SSZ+HCQ > MTX (modified ACR 50 improvement after 9 months)     |
| Dougados, 1999 (31)              | 209         | 12                      | DMARD-naïve (parallel)  | Early RA       | Up to 15                | MTX vs. SSZ vs. MTX+SSZ         | MTX+SSZ = MTX*   |
| Kremer, 2002 (14)                | 263         | 6                       | MTX-IR (step-up)        | Established RA | 16.1–16.8               | MTX vs. MTX+LEF                 | MTX+LEF > MTX (ACR20 at week 24)   |
| Marchesoni, 2003 (24)            | 61          | 12                      | DMARD-naïve (parallel)  | Early RA       | 9.5–11.2                | MTX vs. MTX+CSA                 | MTX+CSA > MTX (inflammatory articular symptoms and radiographic progression after 12 months) |
| Lehman, 2005 (29) / METGO trial  | 65          | 12                      | MTX-IR (step-up)        | Established RA | 18.5                    | MTX vs. MTX+intramuscular gold  | MTX+IM gold > MTX (ACR50 and ACR70)  |
| Capell, 2007 (30) / MASCOT study | 165         | 12                      | Non-MTX-IR (step-up)    | Established RA | 12.5–15                 | MTX vs. SSZ vs. MTX+SSZ         | MTX+SSZ > SSZ and MTX+SSZ > MTX (DAS at 18 months)   |

>: was superior to; =: does not show a difference;

\*No significant superiority of the combination therapy although several outcomes were in favour (31).

more effective than either drug alone in patients with rheumatoid arthritis who had experienced a suboptimal response to sulfasalazine (30). In another trial DMARD-naïve RA patients with early ( $\leq 1$  year duration) active disease were randomised to either SSZ 2000 (maximum 3000) mg daily ( $n=68$ ), or MTX 7.5 (maximum 15) mg weekly ( $n=69$ ) or the combination (SSZ + MTX) of both ( $n=68$ ) (31). However, this study did not demonstrate a statistically significant superiority of the combination therapy, although several outcomes were in favour of the combination. The tolerability of the three treatment modalities seemed comparable.

#### **MTX/hydroxychloroquine (HCQ) vs. MTX/SSZ vs. MTX/SSZ/HCQ**

A two-year trial included 171 patients with disease duration of more than six months who had not received DMARD combinations previously; the patients were randomly assigned to a three-drug combination MTX, 7.5 to 17.5 mg per week, sulfasalazine (500 mg to 1000 mg twice daily), and hydroxychloroquine (HCQ, 200 mg twice daily) or to two-drug regimens of either MTX

plus HCQ or MTX plus SSZ (32). The primary end point (ACR20 response at two years) was significantly higher with the three-drug regimen (78 vs. 60 and 49%, respectively). A similar difference was seen for ACR50 responses (55 vs. 40 and 29%, respectively). The likelihood of a response did not appear to differ between patients who were MTX-naïve and those who had previously received MTX but responded inadequately. All treatment regimens were well tolerated.

#### **Triple therapy with MTX + SSZ + HCQ**

Triple therapy with MTX + SSZ + HCQ was evaluated in a double-blind, randomised study of 102 patients with rheumatoid arthritis and poor responses to at least one DMARD (33). Triple therapy with MTX (7.5 to 17.5 mg per week), SSZ (500 mg twice daily) and HCQ (200 mg twice daily) was superior to SSZ plus HCQ or to MTX alone in achieving the primary end point of at least 50% improvement after nine months, with sustained benefit for at least two years without the development of significant drug toxicity (33).

The Finnish RA combination therapy trial FINRACO in DMARD-naïve patients with a 2-years follow-up sought evidence on the efficacy and tolerability of combination therapy (SSZ, MTX, HCQ and prednisolone) compared to treatment with a single DMARD, with or without prednisolone, in patients with early RA (34). The rate of remission was significantly higher in the patients treated with triple therapy and prednisolone at both one year (24.7 vs. 11.2%) and two years (37.1 vs. 18.4%). Initial treatment of early RA with the triple therapy for the first 2 years limited the peripheral joint damage for at least 5 years (35).

#### **Therapeutic strategies and DMARD combinations**

Several clinical trials were set up to investigate the optimal strategy in the treatment of RA.

The FINRACO trial demonstrated that a strategy of initial multidrug combination and adjustment of treatment every 3 months according to the DAS was clearly superior to monotherapy with either MTX or SSZ (34). Recently, the 11-year results of the FINRACO

**Table II.** Characteristic of pivotal strategy trials.

| Strategy trial                         | Sample size | Study duration (months) | Strategy (trial design) | Duration       | MTX mean dose (mg/week) | DMARDs tested   | Outcome  |
|--|-------------|-------------------------|-------------------------|----------------|-------------------------|---|--|
| FINRACO trial (34), Lancet 1999        | 199         | 24                      | DMARD-naïve (parallel)  | Early RA       | 7.5–15                  | MTX+SSZ+HCQ vs. MTX or MTX+SSZ+HCQ vs. SSZ  | MTX+SSZ+HCQ > MTX and MTX+SSZ+HCQ > SSZ                    |
| COBRA trial (41), Arthritis Rheum 2002 | 148         | 60                      | DMARD-naïve             | Early RA       | 7.5                     | MTX+SSZ vs. SSZ   | MTX+SSZ > SSZ  |
| TICORA study (38), Lancet 2004         | 110         | 18                      | Non-MTX-IR (step-up)    | Established RA | 13.6–17.6               | SSZ vs. MTX+SSZ+HCQ   | Patients treated intensively > routine care                |
| BeSt trial (40), Arthritis Rheum 2005  | 508         | 12                      | DMARD-naïve (parallel)  | Early RA       | 15–30                   | Sequential MTX monotherapy vs. step-up combination therapy vs. Initial combination vs. initial MTX+infliximab | initial combination therapy > initial monotherapy groups   |
| CAMERA trial (39), Ann Rheum Dis 2007  | 299         | 24                      | DMARD-naïve             | Early RA       | 7.5–30                  | MTX vs. MTX+CSA   | intensive (tight control) strategy > conventional strategy |
| SWEFOT trial (44), ACR 2008            | 487         | 12                      | MTX-IR (step-up)        | Early RA       | 20                      | MTX+SSZ+HCQ vs. MTX+infliximab  | MTX+infliximab > MTX+SSZ+HCQ                               |

>: was superior to

trial were published. 65 patients in the FINRACO combination and 65 in the monotherapy group had radiographs of hands and feet available at baseline and at 11 years. The mean progression from baseline to 11 years in Larsen score was significantly lower (17 (95% CI, 12 to 26)) in the combination group than in the monotherapy groups (27 (95% CI, 22 to 33) ( $p=0.037$ )) (36). Moreover, safety was comparable in the different treatment arms, in particular with regard to renal toxicity (37).

The TICORA study demonstrated that the concept of tight control with frequent (monthly) visits to the rheumatologist, the generous use of glucocorticoid injections, and the frequent adjustment of therapy according to DAS led to superior results compared to a more conventional approach (38). Compared with routine care, patients treated intensively were more likely to have a good response or achieve remission (disease activity score <1.6; 36/55 [65%] vs. 9/55 [16%], 9.7 [3.9–23.9],  $p<0.0001$ ). Patients in the intensive group were more likely to receive combination DMARD therapy than were those in the routine group (37 [67%] vs. 6 [11%]).

The CAMERA trial (Computer Assisted Management in Early RA) confirmed benefits of early tight control in the management of RA (39). In this

multicentre open label strategy trial, 299 patients with early rheumatoid arthritis were randomly assigned to the intensive strategy group or the conventional strategy group. Patients in both groups received MTX, the aim of treatment being remission. Patients in the intensive treatment group came to the outpatient clinic once every month; adjustment of the MTX dosage was tailored to the individual patient on the basis of predefined response criteria, using a computerised decision program. Patients of the conventional strategy group came to the outpatient clinic once every three months; they were treated according to common practice. Cyclosporine was added if patients had an inadequate response to maximal tolerated MTX doses. In the intensive strategy group and conventional strategy group, cyclosporine was given to 38 and 4 patients respectively as a next step after the maximum (tolerable) dose of MTX was reached. The CAMERA trial therefore confirmed a better clinical efficacy of an intensive (tight control) strategy compared to a conventional strategy.

The BeSt trial compared four different treatment strategies in 508 patients with early active RA (40). Treatment adjustments were made every 3 months in an effort to achieve low disease activity (DAS44  $\leq 2.4$ ). Sequential MTX

monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose prednisone (group 3), and initial combination therapy with infliximab (group 4). The patients assigned to sequential monotherapy (group 1) started with 15 mg/week MTX, which was increased to 25–30 mg/week if the DAS<sub>44</sub> was >2.4. Subsequent steps for patients with an insufficient response were SSZ monotherapy, leflunomide monotherapy followed by MTX with infliximab. The patients assigned to step-up combination therapy (group 2) also started with 15 mg/week MTX, which was increased up to 30 mg/week. In case of an inadequate response, SSZ was added, followed by the addition of HCQ and then prednisone. If Patients still have active disease, they would subsequently be switched to MTX with infliximab. The other two groups started with combination therapy; group 3, initial combination therapy with MTX, SSZ and prednisolone; and group 4, initial combination therapy with MTX and infliximab. The initial combination therapy groups showed an earlier improvement in DAS, HAQ and quality of life, earlier remission and less radiological progression compared to the initial monotherapy groups.

More than 40% of the patients in groups 1 and 2 achieved an clinical response



with MTX monotherapy, which suggests that a large proportion of patients would be overtreated if all patients were to start with initial combination therapy. On the other hand, the patients in groups 3 and 4 had the benefit of a more rapid relief of symptoms and improvement of physical function. In addition, effective suppression of disease activity during the early phases of the disease may ameliorate the long-term joint damage and prevent poor physical function (40).

The group 3 strategy in the BeSt trial was designed according to the COBRA trial. The COBRA trial was the first study to compare a step-down approach using DMARD combination to SSZ alone. The combination of MTX, SSZ and high dose prednisolone (rapidly tapered) was more effective than SSZ alone, with a better clinical response and significantly less progression of joint damage during 5 years of follow-up (41). A recent update on radiological progression after 11 years showed that this benefit was subsequently lost, possibly because of the unequal drop-out rates in both groups (42, 43).

Recently the SWEFOT trial was designed to compare two treatment strategies for patients with early rheumatoid arthritis. All patients started treatment with MTX (up to 20mg/week) and were evaluated after 3–4 months. Patients who did not achieve low disease activity (DAS28 <3.2) were randomised to receive either SSZ and HCQ or infliximab in addition to MTX (44). After 1 year, patients who received MTX/infliximab combination had significantly higher remission rates (42 vs. 26%) and higher ACR50 and 70 responses (29 and 13%, 16 and 8%, respectively) than patients who received the combination of conventional DMARDs. Interestingly, after 2 years the difference with regard to clinical outcome was no longer statistically significant. In contrast, radiographic progression was significantly more pronounced in the group of patients who received conventional treatment.

In conclusion, the use of MTX in combination with other DMARDs may still represent a valuable therapeutic option in patients who fail to DMARD mono-

therapy or in whom combination therapy is considered initially. However, in patients at risk for rapid radiographic progression, the present data supports the early use of biologics in patients who fail to MTX.

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