Low-Dose Prednisone Inclusion in a Methotrexate-Based, Tight Control Strategy for Early Rheumatoid Arthritis

A Randomized Trial

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Background: Treatment strategies for tight control of early rheumatoid arthritis (RA) are highly effective but can be improved.

Objective: To investigate whether adding prednisone, 10 mg/d, at the start of a methotrexate (MTX)–based treatment strategy for tight control in early RA increases its effectiveness.

Design: A 2-year, prospective, randomized, placebo-controlled, double-blind, multicenter trial (CAMERA-II [Computer Assisted Management in Early Rheumatoid Arthritis trial-II]). (International Standard Randomised Controlled Trial Number: ISRCTN 70365169)

Setting: 7 hospitals in the Netherlands.

Patients: 236 patients with early RA (duration <1 year).

Intervention: Patients were randomly assigned to an MTX-based, tight control strategy starting with either MTX and prednisone or MTX and placebo. Methotrexate treatment was tailored to the individual patient at monthly visits on the basis of predefined response criteria aiming for remission.

Measurements: The primary outcome was radiographic erosive joint damage after 2 years. Secondary outcomes included response criteria, remission, and the need to add cyclosporine or a biologic agent to the treatment.

Results: Erosive joint damage after 2 years was limited and less in the group receiving MTX and prednisone (n = 117) than in the group receiving MTX and placebo (n = 119). The MTX and prednisone strategy was also more effective in reducing disease activity and physical disability, achieving sustained remission, and avoiding the addition of cyclosporine or biologic treatment. Adverse events were similar in both groups, but some occurred less in the MTX and prednisone group.

Limitation: A tight control strategy for RA implies monthly visits to an outpatient clinic, which is not always feasible.

Conclusion: Inclusion of low-dose prednisone in an MTX-based treatment strategy for tight control in early RA improves patient outcomes.

Primary Funding Source: Catharijne Foundation.

Rheumatoid arthritis (RA) should ideally be treated as soon as possible after diagnosis, when it is believed to be most responsive to treatment, the “window of opportunity” (1–4). Both short- and long-term prognoses are better if remission (that is, the absence of symptoms and signs) is induced early in the disease course (5, 6). This can be achieved by using tight control treatment strategies tailored to the RA activity of an individual patient by dosage and medication adjustments (“tight control”) (7–9) and aimed to achieve a predefined level of low disease activity, preferably remission (“treat to target”) within a limited period (8).

Both step-down strategies (starting with combination treatment with disease-modifying antirheumatic drugs [DMARDs], tapering down in case of clinical response) (6, 10) and step-up strategies (starting 1 DMARD and adding DMARDs in case of insufficient effect) have been shown to be effective (11). Step-down strategies use the window of opportunity optimally with quick symptom relief for patients but can result in overtreatment. In contrast, medication in step-up strategies can be tailored to the disease activity of the individual patient without overtreatment; however, the window of opportunity may be used less efficiently, and symptom relief may be slower than with step-down strategies (12).

Methotrexate (MTX) is known as an anchor drug, because it is the most common and effective conventional DMARD for RA. It is cheap, effective, relatively fast-acting, and well-tolerated. It slows joint damage and can be administered orally and subcutaneously in a relatively wide dosage range (2.5 to 30.0 mg/wk) (13–16).

The previous CAMERA (Computer Assisted Management in Early Rheumatoid Arthritis) study (17) applied...
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Context
When methotrexate (MTX) is used as initial therapy for rheumatoid arthritis (RA), additional disease-modifying antirheumatic drugs (DMARDs) must frequently be added to achieve optimal outcomes.

Contribution
Patients with RA were randomly assigned to receive MTX plus low-dose prednisone or MTX plus placebo. Response was measured frequently, and, if inadequate, another DMARD was added. Patients who received MTX plus prednisone had less erosive joint damage and were more likely to achieve remission and less likely to require additional DMARDs than those who began treatment with MTX plus placebo.

Caution
The trial was not powered to compare adverse effects, including infection.

Implication
Initial treatment for RA with low-dose prednisone plus MTX may result in improved outcomes.

—The Editors

MTX in a step-up tight control strategy and showed increased effectiveness compared with a usual care strategy with MTX. In the tight control group, 50% of participants experienced at least 1 period of remission compared with 37% in the usual care group. In an earlier randomized clinical trial by our group, prednisone, 10 mg/d, was shown to slow progression of radiographic joint damage in patients with early RA (18). This result and those of other studies helped to conclude that prednisone is a DMARD (19).

Glucocorticoids inhibit, among other inflammatory mechanisms, the cytokine-induced production of the receptor activator of nuclear factor-κB ligand, which activates osteoclasts (20). This is why prednisone particularly reduces bone erosion in inflamed joints (21).

However, previous studies showing a DMARD effect of glucocorticoids did not apply tight control DMARD strategies. We examined whether prednisone added at the start of an MTX-based, tight control DMARD strategy for early RA would still have additional disease-modifying properties, that is, inhibition of erosive joint damage, as a primary aim. As a secondary aim, we investigated whether the strategy with prednisone would be more effective clinically than the same strategy without prednisone.

Methods
Design Overview
From 2003 until 2008, patients with early RA who fulfilled the 1987 revised American College of Rheumatology (ACR) criteria (22) were eligible for this randomized, placebo-controlled, double-blind, prospective, multicenter, 2-year, tight control strategy trial, CAMERA-II. The medical research ethics committee of all involved hospitals approved the study. All consecutive patients who visited the outpatient clinic of 1 of the 7 rheumatology departments in the region of Utrecht, the Netherlands, collaborating in the Utrecht Rheumatoid Arthritis Cohort study group, were asked to participate, and patients gave written informed consent before entering the study.

Setting and Participants
Inclusion criteria were disease duration less than 1 year, age older than 18 years, and a DMARD- and glucocorticoid-naïve status. Exclusion criteria were creatinine clearance by using the Cockcroft-Gault equation of less than 75 mL/min per 1.73 m², aspartate and alanine aminotransferase levels greater than twice the upper limit of normal, active or recent hepatitis or cirrhosis, malignant tumors, inadequately controlled diabetes mellitus or arterial hypertension, serious infections, serious cardiac or respiratory diseases, leukopenia or thrombocytopenia, inadequate contraception, pregnancy, breastfeeding, osteoporosis, use of cytotoxic or immunosuppressive drugs for 3 months before inclusion, current or past substance abuse or alcohol use greater than 2 U/d, and psychological illnesses or intellectual disorders that would preclude adherence to the study protocol.

Randomization and Intervention
The pharmacy of the University Medical Center Utrecht (UMCU) randomly assigned participants to the tight control, MTX-based treatment strategy combined with either low-dose prednisone, 10 mg/d (MTX and prednisone group), or placebo (MTX and placebo group) in blocks of 4 patients stratified for each clinic. The pharmacy provided the placebo tablets, which were similar in appearance and taste to the prednisone tablets and stored at blinded local pharmacies of the participating hospitals.

The trial coordinator at UMCU performed the logistics. Everyone was blinded except the pharmacist at UMCU. Unblinding was done at the end of the study by the pharmacist at UMCU or in an earlier phase of the study in case of withdrawal due to severe adverse events or to surgery if glucocorticoid stress schemes would be indicated for patients receiving prednisone.

Treatment Strategies
The tight control, MTX-based treatment strategy comprised an initial dosage of oral MTX, 10 mg/wk, with folic acid, 0.5 mg/d, except for the day of MTX intake. All patients received a bisphosphonate (alendronate or risedronate) and a calcium carbonate preparation with vitamin D (cholecalciferol). Use of nonsteroidal anti-inflammatory drugs was allowed, but intra-articular injections were avoided as much as possible and recorded when given.

At each monthly visit, the rheumatologist assessed and entered into a computer the swollen joint count; tender joint count; erythrocyte sedimentation rate (ESR); and visual analogue scale (VAS) for general well-being (0 to 100...
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Outcomes and Follow-up

Assessments

At baseline and subsequent monthly visits, investigators assessed the following disease activity variables: swollen joint count (range, 0 to 38 joints), tender joint count (range, 0 to 38 joints), VAS pain score (mean VAS pain score at night and in the morning, 0 to 100 mm, with 100 mm signifying the worst possible pain), VAS general well-being score (0 to 100 mm, with 100 mm signifying the worst score), ESR (range, 1 to 140 mm/h), C-reactive protein level (normal, <10 mg/L), and duration of morning stiffness (range, 0 to 180 min).

Investigators calculated the Disease Activity Score 28 (DAS28), which is an index for disease activity (range, 0 to 9.3, with 9.3 signifying the highest disease activity) based on the tender and swollen joint counts of 28 joints, the ESR, and the VAS score for general well-being (23). Every 3 months, they also assessed the Health Assessment Questionnaire (HAQ) score (Dutch version) (24), which measured physical disability (range, 0 to 3, with 3 signifying the highest level of disability).

At baseline, investigators recorded rheumatoid factor status as positive or negative. Screening studies at baseline included serum albumin levels, titers of hepatitis B surface antigen and anti–hepatitis C virus antibodies, serum and urine glucose levels, radiography of the chest and thoracic and lumbar spine, and bone densitometry (which was repeated annually). The hands and feet were radiographed at inclusion and annually thereafter.

Primary Outcome

The primary outcome was erosive radiographic joint damage at 2 years. Radiographs were scored by 2 readers in chronologic order at the end of the trial according to the Sharp–van der Heijde score (SHS) for erosions (range, 0 to 280), which was the primary outcome of the trial. In addition, the SHS for joint-space narrowing (JSN) (range, 0 to 168) was assessed; the sum of the erosion and JSN scores was the total SHS (range, 0 to 448) (25). In case of disagreement, consensus between the 2 observers determined the final scores. Both readers were blinded to patient characteristics and treatment strategy.

Secondary Outcomes

Secondary outcome measures were individual variables of disease activity over time, the number of patients satisfying the ACR and the European League Against Rheumatism (EULAR) response criteria at 1 and 2 years (Appendix Tables 1 and 2, available at www.annals.org), number of patients in sustained remission as defined earlier (Appendix Figure) at any time during the trial, duration of remission, time until first remission, the number of patients who needed subcutaneous MTX or cyclosporine or adalimumab treatment, and the number of intra-articular injections during the trial.

Adverse Events

A standard list of adverse events known to be related to prednisone (26) or MTX therapy was used to record adverse events at every visit, according to protocol. Other adverse events could also be recorded on this list. Severe adverse events were defined as any untoward medical occurrence that resulted in hospitalization or death.

Statistical Analysis

The statistical software SPSS 17.0 (SPSS, Chicago, Illinois) and SAS, version 9.1 (SAS Institute, Cary, North Carolina), were used for analyses of data. A P value of less than 0.05 was considered to be statistically significant.
Sample size calculations were based on a previous study by our group (18), which showed mean erosive radiographic joint damage at 2 years of 16 (SD, 20) in the prednisone group versus 29 (SD, 30) in the placebo group. Assuming that intensive concomitant treatment with MTX in this study would reduce erosion at 2 years in both groups to 30% of the damage, as found in our previous study (18), the expected erosion score in the MTX and prednisone group would be 4.8 (SD, 6) versus 8.7 (SD, 10) in the MTX and placebo group. On the basis of these assumptions and to allow for withdrawals, more than 100 patients in each group would be adequate to reach significance (α < 0.05) by using a power of 0.80.

For the primary outcome (radiographic erosive joint damage) and all disease activity variables, 5 imputed data sets were generated (multiple imputations) by using a fully conditional specified model to handle missing values, which were considered to be missing at random. Imputations were based on baseline characteristics (that is, randomization, study center, age, and sex) and known predictors (that is, rheumatoid factor status, baseline DAS28 and radiographic joint damage, and use of subsequent strategy treatments).

Pooled estimates from these 5 imputed data sets were reported in the results. All analyses were performed on the imputed data, and only secondary analyses were performed on the observed data. For the categorical secondary outcomes (ACR and EULAR response criteria, number of patients in sustained remission, and number of patients who needed subcutaneous MTX or cyclosporine or adalimumab treatment or intra-articular injections), patients who withdrew were considered nonresponders. Appendix Tables 1 and 2 define nonresponders for the ACR and EULAR response criteria.

Testing for significance of differences in erosion scores between the 2 groups at 2 years was done by using the Mann–Whitney U test and was based on a longitudinal regression analysis (linear mixed model), which was performed by using treatment strategy, time, and the interaction term of time and treatment as independent variables and the erosion score as a dependent variable; baseline erosion score, rheumatoid factor status, and study center were covariates. Erosion scores were not normally distributed; however, after correction for baseline erosion score and other covariates in the model, the residual variance of the model was nearly normally distributed and symmetrical, indicating that the results of the analysis were valid. In addition, differences in the JSN score and total SHS between the 2 groups at 2 years were tested by using Mann–Whitney U tests.

For the secondary outcomes regarding disease activity variables, longitudinal regression analyses (linear mixed model) were performed by using treatment strategy, time, and the interaction term of time and treatment as independent variables and the disease activity variable as the dependent variable; the baseline disease activity variable, rheumatoid factor status, and study center were covariates. In addition, testing of differences between the 2 groups in means at specific points in time was based on the longitudinal data analysis for the DAS28 and on independent t tests for other secondary outcomes. Differences in categorical outcomes (that is, ACR and EULAR response criteria, number of patients in sustained remission, number of patients who needed subcutaneous MTX or cyclosporine or adalimumab treatment, and number of intra-articular injections) were tested by using chi-square and Fisher exact tests; the difference in duration and time until sustained remission between the 2 groups was tested by using logrank tests.

Differences in adverse events between the treatment groups in mean values of continuous adverse effects data (that is, nonfasting serum glucose levels and weight gain during the trial) were tested by using independent t tests and differences in categorical data with chi-square and Fisher exact tests (for example, the number of adverse events and the number of patients with an increase in glucose levels >1.0 mmol/L [>18 mg/dL] compared with baseline). The occurrence of adverse events and severe adverse events was investigated on the patient level between both treatment groups; each patient could have more than 1 adverse event. Sensitivity analyses were performed for the primary outcome regarding missing data and dropouts. The missing data (including dropouts) for erosive joint damage after 2 years of treatment were imputed with the 80th percentile of erosive damage of the respective treatment strategy to investigate the effects on statistical results if missing data would have been more frequently present in patients with worse results.

Role of the Funding Source

The Catharijne Foundation funding organization was not involved in study design, data collection, data analysis, data interpretation, writing of this report, or the decision to submit the manuscript for publication. The corresponding author had full access to trial data and had final responsibility for the decision to submit for publication.

Results

Table 1 shows the baseline characteristics of the 2 groups (total of 236 patients). During the study, 32 patients in the MTX and prednisone group and 34 patients in the MTX and placebo group withdrew (Figure 1): 85 patients in each treatment group completed the 2-year trial. The median follow-up for the MTX and prednisone group was 25.2 months (interquartile range [IQR], 23.9 to 26.7 months) versus 25.5 months (IQR, 24.4 to 26.5 months) for the MTX and placebo group (P = 0.68).

Primary Outcome

Erosive joint damage after 2 years was limited and significantly less in the MTX and prednisone group (median, 0 [IQR, 0 to 0]) than in the MTX and placebo group.
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ORIGINAL RESEARCH

Table 1. Baseline Demographic and Clinical Characteristics of Patients in the CAMERA-II Trial*

<table>
<thead>
<tr>
<th>Characteristic†</th>
<th>Treatment Strategy</th>
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<tbody>
<tr>
<td></td>
<td>MTX and Prednisone (n = 117)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>70 (60)</td>
</tr>
<tr>
<td>Rheumatoid factor–positive status, n (%)</td>
<td>64 (55)</td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td>54 (14)</td>
</tr>
<tr>
<td>Mean morning stiffness (SD), mm</td>
<td>87 (53)</td>
</tr>
<tr>
<td>Mean ESR (SD), mm/h</td>
<td>36 (25)</td>
</tr>
<tr>
<td>Mean CRP level (SD), mg/L</td>
<td>31 (35)</td>
</tr>
<tr>
<td>Radiographic damage present, n (%)</td>
<td>34 (29)</td>
</tr>
<tr>
<td>Erosions present, n (%)</td>
<td>20 (17)</td>
</tr>
<tr>
<td>Joint-space narrowing present, n (%)</td>
<td>25 (21)</td>
</tr>
<tr>
<td>Median total SHS (IQR)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Median SHS for erosions (IQR)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Median SHS for joint-space narrowing (IQR)</td>
<td>0 (0–0)</td>
</tr>
</tbody>
</table>

CRP = C-reactive protein; DAS28 = Disease Activity Score assessing 28 joints, ESR, and CRP for general well-being; ESR = erythrocyte sedimentation rate; HAQ = Health Assessment Questionnaire; IQR = interquartile range; MTX = methotrexate; SHS = Sharp–van der Heijde score; VAS = visual analogue scale.† Of all patients, study center 1 included 31 patients in the MTX and prednisone group and 29 in the MTX and placebo group. This was, respectively, 21 and 22 patients for center 2; 19 and 21 for center 3; 26 and 27 for center 4; 11 and 9 for center 5; 8 and 10 for center 6; and 1 and 1 for center 7.

(median, 0 [IQR, 0 to 2]) (P = 0.022); the difference between median erosive joint damage was 0.0 (95% CI, −0.1 to 0.0). The cumulative probability plot on erosion scores at 2 years (Figure 2) shows that 78% of all patients in the MTX and prednisone group versus 67% in the MTX and placebo group were still erosion-free; of those who did have erosion, erosion scores were higher in the MTX and placebo group. On the basis of the linear mixed-model analysis, erosion score at 2 years was on average 0.87 SHS units lower in the MTX and prednisone group than in the MTX and placebo group (regression coefficient, −0.87 [CI, −1.31 to −0.43]; P = 0.001). Sensitivity analyses for the primary outcome (erosive joint damage after 2 years of treatment) for missing data (16% of total) and withdrawals showed no differences in the statistical significance of results (data not shown).

We also examined other radiographic scores. The JSN score and total SHS at 2 years were not different. The median JSN score at 2 years was 0 (IQR, 0 to 2) in the MTX and prednisone group and 0 (IQR, 0 to 2) in the MTX and placebo group (P = 0.70); these values were 0 (IQR, 0 to 3) and 0 (IQR, 0 to 4) respectively, for the total SHS (P = 0.32). The differences between the median values were 0.0 (CI, 0.0 to 0.0) and 0.0 (CI, −1.1 to 1.1), respectively.

Analyses performed on observed data for the primary outcome, JSN and total SHS, showed similar results (data not shown).

Secondary Outcomes

Disease activity variables after 2 years of treatment improved more, on average, in the MTX and prednisone group than in the MTX and placebo group. Figure 3 shows the course of the variables DAS28, ESR, VAS pain score, and HAQ score during the trial. Improvement was more rapid in the MTX and prednisone group, but the differences observed in the first months decreased over time (Appendix Table 3, available at www.annals.org).

When analyzed over time by using longitudinal regression analyses, patients in the MTX and prednisone group had lower disease activity for all disease activity variables than did patients in the MTX and placebo group (P < 0.001 for all) (Figure 3). According to the regression analysis for the DAS28 at 3 months, the mean difference was −1.56 (CI, −1.88 to −1.25). This value was −0.89 (CI, −0.52 to −0.11) at 6 months, 0.21 (CI, −0.52 to 0.11) at 1 year, and −0.26 (CI, −0.68 to 0.16) at 2 years.

The response rates after 1 year of treatment for the MTX and prednisone group and the MTX and placebo group for the ACR20 response criteria, that is, the percentages of patients with at least 20% improvement, were 70% versus 66% (P = 0.45); they were 56% versus 43% (P = 0.037) for the ACR50 criteria (at least 50% improvement) and 27% versus 26% (P = 0.82) for the ACR70 criteria (at least 70% improvement). Similar differences were seen after 2 years: These response rates were 65% versus 61% (P = 0.56) for the ACR20, 53% versus 42% (P = 0.091) for the ACR50, and 38% versus 19% (P = 0.002) for the ACR70. The EULAR response criteria showed no significant differences between the 2 treatment groups (Appendix Table 3).

Remission lasted an average of 10 months (SD, 6) in the patients in both groups who reached remission. However, time until the first sustained remission was shorter in the MTX and prednisone group (11 months [SD, 5]; P = 0.001). A somewhat higher number of patients had at least 1 sustained remission in the MTX and prednisone group (n = 84 [72%]) than in the MTX and placebo group (n = 73 [61%]) (P = 0.089).

In the MTX and prednisone group, 26 patients (22%) needed the subcutaneous MTX treatment compared with 60 patients (50%) in the MTX and placebo group (P < 0.001). The mean of maximum dosages of MTX (oral or subcutaneous) in individual patients during the trial was 19.7 mg/wk (SD, 6.1) and for the MTX and prednisone group 23.4 mg/wk (SD, 4.5) for the MTX and placebo group (P < 0.001).
Eighteen patients (15%) in the MTX and prednisone group versus 49 patients (41%) ($P < 0.001$) in the MTX and placebo group also needed a subsequent treatment after the last MTX step; 2 versus 7 of the patients used cyclosporine (before the protocol amendment) added to MTX and 16 versus 42 used adalimumab. The mean period between the start of the study and the start of this treatment was 14 months (SD, 6) for the MTX and prednisone group versus 12 months (SD, 6) for the MTX and placebo group ($P = 0.18$).

Cyclosporine was used in the MTX and prednisone group an average of 12 months (SD, 6) versus 9 months (SD, 9) in the MTX and placebo group; adalimumab was used in the MTX and prednisone group an average of 13 months (SD, 6) versus 12 months (SD, 6) in the MTX and placebo group. The proportion of patients who received 1 or more intra-articular injections during the study was 25% in the MTX and prednisone group and 36% in the MTX and placebo group ($P = 0.066$). Analyses of observed data yielded similar results (data not shown).

**Adverse Events**

Sixteen patients (14%) in the MTX and prednisone group and 20 patients (17%) in the MTX and placebo group withdrew from the study because of adverse events; 1 patient in the MTX and prednisone group withdrew because of surgery, and 1 patient in the MTX and prednisone group died of causes unrelated to the medication (Table 2). Adverse events resulting in withdrawal were vertebral fracture, cough, headache, dizziness, loss of clear-
headedness, liver function disorders, diarrhea, constipation, nausea, weight gain, hypertension, hair loss, dry eyes, and blurred vision for the MTX and prednisone group and pericarditis, ketoacidosis, pneumonia, persistent respiratory infection, (severe) headache, a blocked shunt in the brain, loss of clearheadedness, nausea, tiredness, liver function disorders, diarrhea, stomachache, glaucoma, and mouth ulcers for the MTX and placebo group.

Patients who withdrew may have had more than 1 adverse event, and several of the adverse events listed above may have occurred in more than 1 patient. There were no clinically important differences in number and type of adverse events leading to withdrawal between the first and second year of the trial.

At least 1 adverse event was recorded in 86 patients (74%) in the MTX and prednisone group versus 94 patients (79%) in the MTX and placebo group. Table 2 shows the nature and percentage of adverse events in both groups. Adverse events occurred most often in the central nervous (for example, headache and dizziness), gastrointestinal, and mucocutaneous systems.

Analyzing the number of patients experiencing a sole adverse event at least once during the study showed that patients in the MTX and prednisone group less often had nausea (P = 0.006) and alanine and aspartate aminotransferase levels above the upper limit of normal (P = 0.006 and 0.016, respectively) than did patients in the MTX and placebo group. There were no differences between the groups in numbers of patients having other adverse events (Table 2).

Nonfasting serum glucose levels after 2 years were on average 5.7 mmol/L (SD, 1.4) in the MTX and prednisone group and 5.6 mmol/L (SD, 1.5) in the MTX and placebo group (P = 0.55). Thirteen patients (11%) in the MTX and prednisone group had higher (≥1.0 mmol/L [≥18 mg/dL]) glucose levels at 2 years compared with baseline values versus 9 patients (8%) in the MTX and placebo group. In both groups, 1 patient developed diabetes (Table 2). On average, patients in the MTX and prednisone group gained 2.9 kg (SD, 4.2) in weight during the 2 years compared with baseline versus 1.3 kg (SD, 5.3) for the MTX and placebo group (P = 0.028).
mission, tapering down treatment) were dictated by a composite of the same variables that form the EULAR response criteria. For the difference in improvement in clinical variables and acute-phase response between both strategies in favor of the MTX and prednisone strategy, one could argue that prednisone has nonspecific positive effects. However, similar improvements in swollen joint counts assessed by the rheumatologist, physical functioning (for example, the HAQ score), and less erosive joint damage refute a nonspecific effect.

The results from the present study support implementation of a tight control, rapid step-up strategy with MTX plus low to moderate doses of prednisone during the first 2 years of the disease. In this respect, our data corroborate the recently published EULAR guidelines on treatment of RA (4). Although a large proportion of patients in the MTX and placebo group also did not need biologic therapy during the first 2 years of their disease, patients in the MTX and placebo strategy had a slower clinical response and less favorable outcome on all variables than those in the MTX and prednisone group, including physical functioning and quality of life. This, along with the finding that the MTX and prednisone strategy was not associated with more adverse effects, suggests that treating patients with glucocorticoids during the first 2 years of the disease is

**Figure 3.** Course of disease activity variables during 2 years of treatment, based on pooled results of imputed analyses.

DAS28 = Disease Activity Score assessing 28 joints (range, 0 to 9.3 [highest disease activity]); ESR = erythrocyte sedimentation rate (range, 1 to 140 mm/h); HAQ = Health Assessment Questionnaire (range, 0 to 3 [most physical disability]); MTX = methotrexate; VAS = visual analogue scale (range, 0 to 100 mm [worst status]).

* Significant differences between both treatment strategies at 3 mo, 6 mo, 1 y, 18 mo, or 2 y of treatment.

† P values are based on differences between both treatment strategies evaluated with longitudinal regression analyses.
a better option; thereafter, prednisone therapy should be tapered and stopped, if possible.

This suggestion would be different if prednisone therapy would have to be continued for several years or if we could reliably predict which individual patients would not develop joint damage and would fare well with MTX alone; however, this prediction has been extensively investigated and until now has failed. Furthermore, adding prednisone if MTX does not adequately control the disease would not optimally make use of the window of opportunity—the period very early in the disease course during which RA is believed to be most responsive to treatment—and the effects of this strategy are not known.

We found a reduced need for additional treatments, notably biologic agents, during the first 2 years of RA in the MTX and prednisone group, which could, along with better current (and possibly future) physical functioning and quality of life, affect cost-effectiveness (28–30). A recently published EULAR paper on the economic aspects of treatment options in RA supports the concept of an early start of traditional DMARDs and rapid treatment escalation if response is insufficient rather than starting with biologic agents (30). A recent meta-analysis suggested that combination treatment with conventional DMARDs and glucocorticoids might be as effective in reducing joint destruction as the more expensive combination of biologic agents with MTX (31).

On the basis of these data, a cost-effectiveness trial comparing a tight control strategy of MTX and prednisone with a strategy directly starting with a biologic agent seems justified. Results of this study would be of special interest to clinicians in developing countries, where biologic agents are less available.

The 10-mg/d dosage of prednisone can be considered low to moderate and is associated with low risks for adverse events in patients with RA (32). It is surprising that, although our study was not powered to analyze differences between groups regarding specific adverse events, elevated serum aminotransferase levels and nausea occurred significantly less frequently in the MTX and prednisone group. An explanation could be that the average maximum dosage of MTX in the group was lower.

In addition, because of higher disease activity, nonsteroidal anti-inflammatory drugs in the MTX and placebo group might have been used more intensively than in the MTX and prednisone group, similar to our findings in another study (33). However, we did not systematically record nonsteroidal anti-inflammatory drug use in this study, so the latter is a hypothesis. The difference in weight gain between the groups can be attributed to prednisone, but may also partly result from earlier and better control of disease activity over time (34); however, this also is a hypothesis.

No study has evaluated the additional joint-protective effect of continuing glucocorticoids 2 years after a diagnosis of RA (19). Thus, it would make sense to taper and stop glucocorticoid therapy after this period, if possible, especially because some adverse events (such as osteoporosis) are associated with long-term use of glucocorticoids.

In conclusion, including low-dose prednisone from the start of a tight control, MTX-based treatment strategy for early RA for 2 years after the diagnosis decreases pro-

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Table 2. Adverse Events During the Trial*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>MTX and Prednisone (n = 117)</th>
<th>MTX and Placebo (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse event, n (%)†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2 (2)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Total patients with ≥1 adverse event, n (%)</strong></td>
<td>86 (74)</td>
<td>94 (79)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse event, n‡</th>
<th>MTX and Prednisone (n = 117)</th>
<th>MTX and Placebo (n = 119)</th>
</tr>
</thead>
</table>

Table 2. Adverse Events During the Trial*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>MTX and Prednisone (n = 117)</th>
<th>MTX and Placebo (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse event, n (%)†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2 (2)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Total patients with ≥1 adverse event, n (%)</strong></td>
<td>86 (74)</td>
<td>94 (79)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse event, n‡</th>
<th>MTX and Prednisone (n = 117)</th>
<th>MTX and Placebo (n = 119)</th>
</tr>
</thead>
</table>

MTX = methotrexate; ULN = upper limit of normal.

* Not all individual adverse events are named, only the most frequent ones per category.
† One death due to coronary syndrome complicated by pulmonary embolism unrelated to the medication. Reasons for hospitalization: vertebral fracture (MTX and prednisone group); pericarditis, ketotacidosis, pneumonia, severe headache, and a blocked shunt in the brain (all in the MTX and placebo group). All hospitalized patients dropped out of the study.
‡ Number of patients with a specific adverse event at least once during the study.
§ One patient could have more than 1 adverse event.
¶ A combination of both alanine and aspartate aminotransferase levels >ULN during the same visit occurred in 15 patients in the MTX and prednisone group and 36 patients in the MTX and placebo group.
∥ Newly developed hypertension was defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg.
¶¶ Newly developed diabetes mellitus was defined as nonfasting serum glucose levels >11.0 mmol/L (≥198 mg/dL).
gession of erosive joint damage, disease activity, physical disability, the need for (early) treatment with cyclosporine or biologic agents, and toxicity.

From the Department of Rheumatology and Clinical Immunology and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, and Diakonessenhuis, Utrecht; St. Antonius Hospital, Nieuwegein; Meander Medical Center, Amersfoort; Tergooi Hospital, Hilversum; St. Janasd Hospital, Harderwijk; and Flevohospital, Almere, the Netherlands.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-0297.

Reproducible Research Statement: Study protocol and statistical code: Available from Dr. Jacobs (e-mail, j.w.g.jacobs@umcutrecht.nl). Data set: Available after establishing an agreement on cooperation.

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References


27. Schett G, Saag KG, Bijlsma JW. From bone biology to clinical outcome:


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Obtaining of funding: J.W.J. Bijlsma.

Appendix Table 1. ACR Response Criteria

ACR20 is ≥20% improvement compared with baseline
ACR50 is ≥50% improvement compared with baseline
ACR70 is ≥70% improvement compared with baseline
Nonresponders are those patients who did not meet ACR20*
Improvement is defined as ≥20%, ≥50%, or ≥70% improvement in tender joint count AND swollen joint count AND ≥3 of the following 5 variables‡:
- Patients’ assessment of pain‡
- Patients’ global assessment of disease activity‡
- Physicians’ global assessment of disease activity‡
- Patients’ assessed physical function, for example, by using the Health Assessment Questionnaire
- Acute-phase reactant value (ESR or CRP)

ACR = American College of Rheumatology; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.
* Nonresponders are patients classified as having no improvement or response.
‡ AND refers to the Boolean operator.
‡ For example, on a visual analogue scale.

Appendix Table 2. European League Against Rheumatism Response Criteria, by using the DAS28

<table>
<thead>
<tr>
<th>DAS28 at End Point</th>
<th>Improvement in DAS28 From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;1.2</td>
</tr>
<tr>
<td>≤3.2</td>
<td>Good</td>
</tr>
<tr>
<td>&gt;3.2 and ≤5.1</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt;5.1</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

DAS28 = Disease Activity Score assessing 28 joints.
Appendix Figure. Study flow diagram showing treatment strategy steps and criteria.

Starting dose of MTX, 10 mg/wk, plus prednisone, 10 mg/d, or placebo = trial medication.

- >20% improvement* at monthly visits
  - Yes: Stepwise increase of MTX by 5 mg/wk to maximum of 30 mg/wk or highest tolerable dose
  - No: Maximum (tolerable) dose and neither remission nor >20% improvement

Medication unchanged; if no >20% improvement at next visits, resume stepping up

Remission for at least 12 wk (sustained remission)

Stepwise decrease of MTX by 2.5 mg/wk; at MTX 10 mg/wk, halve trial medication, then resume stepwise decrease of MTX to 5 mg/wk, then stop trial medication, then resume stepwise decrease of MTX to 0

If remission does not continue

Resume intensifying medication

>20% improvement

Same dose of MTX subcutaneously

Subcutaneous MTX (same dose) + cyclosporine†, starting dose of 2.5 mg/kg daily, stepwise monthly increase of 0.5 mg/kg daily until a maximum of 4 mg/kg daily in case >20% improvement does not continue or Subcutaneous MTX (same dose) + adalimumab†, starting dose of 40 mg every 2 wk

Maximum (tolerable) dose and no remission

Other medication (dropout)

Maximum (tolerable) dose and neither remission nor >20% improvement

Neither remission nor >20% improvement

The start of the treatment strategy (i.e., MTX, 10 mg/wk, in combination with prednisone, 10 mg/d, or placebo) and all possible subsequent steps of the described treatment strategy are shown. Each visit, if the patient had not improved >20% in swollen joint count and at least 2 of the following: tender joint count, erythrocyte sedimentation rate, and visual analogue scale for general well-being, compared with the previous visit (see the Methods section for details). The next step in the strategy was according to this diagram. MTX = methotrexate.

* Defined as (compared with the previous visit 4 wk ago) >20% improvement of number of swollen joints and of ≥2 out of 3 criteria: number of tender joints, erythrocyte sedimentation rate, and visual analogue scale for general well-being. In case of no >20% improvement: stepwise increment in MTX dosage or add and step up of other medication, according to scheme; in case of >20% improvement at a visit, no change in dose of medication at that visit.

† For subcutaneous MTX, as well as oral MTX, each step was applied for ≥4 wk. The criteria for adding cyclosporine or adalimumab as a subsequent treatment strategy step and for stepping up of cyclosporine were the same as for each subcutaneous MTX step. Shortly after starting the trial (after about 20% of inclusions) a protocol amendment was made replacing cyclosporine by adalimumab as the next step, to be added to the maximum subcutaneous MTX dose. The adalimumab dose was increased to 40 mg/wk if the criteria of response were not met after 12 wk. In case of remission for at least 12 wk, the adalimumab dose was reduced to 40 mg every 2 wk and thereafter if persistent remission, the MTX was stepwise reduced.
### Appendix Table 3. Results of Secondary Outcomes, Including Measures of Disease Activity and ACR and EULAR Response Criteria During the Trial*

<table>
<thead>
<tr>
<th>Secondary Outcome</th>
<th>MTX and Prednisone (n = 117)</th>
<th>MTX and Placebo (n = 119)</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACR20, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>82 (70)</td>
<td>78 (66)</td>
<td>4.5 (−7.4 to 16.4)</td>
<td>0.45</td>
</tr>
<tr>
<td>Year 2</td>
<td>76 (65)</td>
<td>73 (61)</td>
<td>3.6 (−8.7 to 15.9)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>ACR50, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>66 (56)</td>
<td>51 (43)</td>
<td>13.6 (0.9 to 26.2)</td>
<td>0.037</td>
</tr>
<tr>
<td>Year 2</td>
<td>62 (53)</td>
<td>50 (42)</td>
<td>11.0 (−1.7 to 23.6)</td>
<td>0.091</td>
</tr>
<tr>
<td><strong>ACR70, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>32 (27)</td>
<td>31 (26)</td>
<td>1.3 (−10.0 to 12.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>Year 2</td>
<td>44 (38)</td>
<td>23 (19)</td>
<td>18.3 (7.0 to 29.6)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>EULAR response year 1, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>75 (65)</td>
<td>75 (63)</td>
<td>11.1 (−11.2 to 13.4)</td>
<td>0.61†</td>
</tr>
<tr>
<td>Moderate</td>
<td>14 (12)</td>
<td>25 (21)</td>
<td>−9.0 (−18.4 to 0.4)</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>27 (23)</td>
<td>19 (16)</td>
<td>7.1 (−3.0 to 17.2)</td>
<td></td>
</tr>
<tr>
<td><strong>EULAR response year 2, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>79 (68)</td>
<td>78 (66)</td>
<td>2.0 (−10.1 to 14.0)</td>
<td>0.809†</td>
</tr>
<tr>
<td>Moderate</td>
<td>8 (7)</td>
<td>16 (13)</td>
<td>−6.6 (−14.3 to 1.0)</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>30 (26)</td>
<td>25 (21)</td>
<td>4.6 (−6.2 to 15.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Remission, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean time in remission (SD), mo</td>
<td>10 (6)</td>
<td>10 (6)</td>
<td>−0.11 (−1.94 to 1.73)</td>
<td>0.91</td>
</tr>
<tr>
<td>Mean time until first remission (SD), mo</td>
<td>6 (5)</td>
<td>11 (5)</td>
<td>−4.43 (−6.16 to −2.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Mean morning stiffness (SD), mm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>50.5 (19.9)</td>
<td>48.2 (14.8)</td>
<td>2.23 (1.01 to 1.09)</td>
<td>0.82</td>
</tr>
<tr>
<td>Year 2</td>
<td>56.1 (25.9)</td>
<td>45.3 (12.5)</td>
<td>10.81 (1.18 to 1.29)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Mean VAS for general well-being (SD), mm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>19.6 (4.9)</td>
<td>22.1 (4.5)</td>
<td>−5.55 (−8.38 to 3.28)</td>
<td>0.42</td>
</tr>
<tr>
<td>Year 2</td>
<td>19.8 (4.7)</td>
<td>23.8 (5.4)</td>
<td>−4.02 (−10.30 to 2.26)</td>
<td>0.206</td>
</tr>
<tr>
<td><strong>Mean VAS for pain (SD), mm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>13.4 (4.0)</td>
<td>14.0 (4.7)</td>
<td>−0.61 (−5.95 to 4.72)</td>
<td>0.80†</td>
</tr>
<tr>
<td>Year 2</td>
<td>11.9 (4.0)</td>
<td>14.6 (4.0)</td>
<td>−2.71 (−7.76 to 2.34)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Mean tender joint count (SD), n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>3.5 (1.3)</td>
<td>3.5 (1.1)</td>
<td>−0.04 (−1.54 to 1.46)</td>
<td>0.96</td>
</tr>
<tr>
<td>Year 2</td>
<td>3.4 (1.3)</td>
<td>3.2 (0.9)</td>
<td>0.18 (−1.19 to 1.55)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Mean swollen joint count (SD), n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>1.9 (0.9)</td>
<td>2.3 (0.9)</td>
<td>−0.39 (−1.36 to 0.58)</td>
<td>0.43</td>
</tr>
<tr>
<td>Year 2</td>
<td>1.2 (0.4)</td>
<td>1.5 (0.4)</td>
<td>−0.33 (−0.90 to 0.26)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Mean HAQ score (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>0.5 (0.11)</td>
<td>0.7 (0.13)</td>
<td>−0.18 (−0.34 to −0.02)</td>
<td>0.027</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.5 (0.13)</td>
<td>0.7 (0.13)</td>
<td>−0.18 (−0.34 to −0.02)</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>Mean DAS28 (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>2.45 (0.29)</td>
<td>2.59 (0.29)</td>
<td>−0.21 (−0.52 to 0.11)</td>
<td>0.194</td>
</tr>
<tr>
<td>Year 2</td>
<td>2.30 (0.34)</td>
<td>2.49 (0.25)</td>
<td>−0.26 (−0.68 to 0.16)</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Mean ESR (SD), mm/h</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>14.6 (2.9)</td>
<td>17.8 (3.4)</td>
<td>−3.21 (−7.15 to 0.73)</td>
<td>0.097</td>
</tr>
<tr>
<td>Year 2</td>
<td>14.4 (2.7)</td>
<td>18.0 (2.9)</td>
<td>−3.61 (−7.09 to −0.13)</td>
<td>0.039</td>
</tr>
<tr>
<td><strong>Mean CRP level (SD), mg/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>5.5 (2.5)</td>
<td>6.3 (2.5)</td>
<td>−0.74 (−3.81 to 2.33)</td>
<td>0.59</td>
</tr>
<tr>
<td>Year 2</td>
<td>5.4 (1.6)</td>
<td>5.6 (2.0)</td>
<td>−0.20 (−2.50 to 2.10)</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>Subcutaneous MTX strategy step, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine or adalimumab strategy step, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CRP level (SD), mg/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous MTX strategy step, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine step 2</td>
<td>18 (15)</td>
<td>49 (41)</td>
<td>−0.26 (−0.38 to −0.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adalimumab strategy step</td>
<td>16</td>
<td>42</td>
<td>−22.5 (−33.1 to −11.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACR = American College of Rheumatology; ACR20 = ≥20% improvement compared with baseline; ACR50 = ≥50% improvement compared with baseline; ACR70 = ≥70% improvement compared with baseline; CRP = C-reactive protein; DAS28 = Disease Activity Score assessing 28 joints; ESR = erythrocyte sedimentation rate; EULAR = European League Against Rheumatism; HAQ = Health Assessment Questionnaire; MTX = methotrexate; VAS = visual analogue scale.

* The measures of the disease activity are based on the pooled results of the imputation analyses (based on 5 imputation sets). VAS range, 0 to 100 mm, with 100 mm signifying the worst status; tender and swollen joint counts range, 0 to 38; HAQ score range, 0 to 3, with 3 signifying the most physical disability; DAS28 range, 0 to 9.3, with 9.3 signifying the highest disease activity; ESR range, 1 to 140 mm/h; normal CRP, <10 mg/L.

† P value for comparison: total patients with EULAR responses (good, moderate, or no response) in the MTX and prednisone group compared with the MTX and placebo group.