Two-Year Clinical and Radiographic Results With Combination
Etanercept–Methotrexate Therapy Versus Monotherapy in
Early Rheumatoid Arthritis

A Two-Year, Double-Blind, Randomized Study

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Objective. To evaluate how continuation of and
alterations to initial year 1 combination etanercept–
methotrexate (MTX) therapy and MTX monotherapy
regimens affect long-term remission and radiographic
progression in early, active rheumatoid arthritis.

Methods. Subjects were randomized at baseline
for the entire 2-year period; those who completed 1 year
of treatment with combination or MTX monotherapy
entered year 2. The original combination group either
continued combination therapy (the EM/EM group; n
1154) or received etanercept monotherapy (the EM/E
group; n 111) in year 2; the original MTX mono-
therapy group either received combination therapy (the
M/EM group; n 90) or continued monotherapy (the
M/M group; n 99) in year 2. Efficacy end points
included remission (a Disease Activity Score in 28 joints
[DAS28] <2.6) and radiographic nonprogression
(change in the modified Sharp/van der Heijde score
<0.5) at year 2. A last observation carried forward
analysis from the modified intention-to-treat population
(n 398) and a post hoc nonresponder imputation
(NRI) analysis (n 528) were performed for remission.

Results. At year 2, DAS28 remission was achieved
by 62/108, 54/108, 51/88, and 33/94 subjects in the
EM/EM, EM/E, M/EM, and M/M groups, respectively
(P < 0.01 for the EM/EM and M/EM groups versus the
M/M group). This effect was corroborated by a more
conservative post hoc 2-year NRI analysis, with remis-
sion observed in 59/131, 50/134, 48/133, and 29/130 of
the same respective groups (P < 0.05 for each of the
EM/EM, EM/E, and M/EM groups versus the M/M
group). The proportions of subjects achieving radio-
graphic nonprogression (n 360) were 89/99, 74/99,
59/79, and 56/83 in the EM/EM (P < 0.01 versus each of

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the other groups), EM/E, M/EM, and M/M groups, respectively. No new safety signals or between-group differences in serious adverse events were seen.

**Conclusion.** Early sustained combination etanercept–MTX therapy was consistently superior to MTX monotherapy. Combination therapy resulted in important clinical and radiographic benefits over 2 study years, without significant additional safety risk.

Over the past decade, strategies for the management of rheumatoid arthritis (RA) have changed substantially with the introduction of goal-driven intensive treatment, the use of potent biologic agents, and the recognition of the importance of earlier treatment (1–4). Although conventional treatment with disease-modifying antirheumatic drugs (DMARDs) is effective in providing clinical and functional benefits in some patients, it may not always be sufficient to halt radiographic progression of joint destruction (1,5–8). In several RA trials, joint damage, as evidenced by radiographic lesions, was found to progress despite intensive conventional DMARD therapy (7–9). Clinical criteria alone may be inadequate measures of remission, which would explain the discrepancy between clinical improvement and progression of joint damage observed in these trials.

Because joint damage has been shown to continue to progress among patients with very limited disease activity, remission is increasingly defined by both clinical and radiographic evidence of disease control.

New treatment strategies consist of earlier, more intensive regimens with combination therapy of several traditional DMARDs or a traditional DMARD and an anti–tumor necrosis factor (anti-TNF) agent to produce the desired clinical responses and prevent joint damage (10). The Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) study found that combination DMARD therapy provided better sustainability of remission than did single DMARD use in patients with early RA, with sustained remission being associated with less radiographic progression (11). Similarly, combination strategy is supported by the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) study, in which a significantly higher percentage of subjects who received 3 years of combination therapy with etanercept plus methotrexate (MTX) had clinical remission of their disease than did those receiving either etanercept or MTX given as monotherapy; moreover, both combination therapy and etanercept monotherapy had significantly greater radiographic efficacy than did MTX monotherapy (12).

The aim of the Combination of Methotrexate and Etanercept in Early Rheumatoid Arthritis (COMET) trial was to evaluate the effects of early intensive therapy with combined treatment on clinical remission (Disease Activity Score in 28 joints [DAS28]; see ref. 13) <2.6) and radiographic progression in subjects with early active RA, merging the combination drug strategy with the concept of early intervention. In the first year of this 2-year, double-blind, randomized study, significantly greater improvements were observed in both disease activity and radiographic outcomes after 52 weeks of combination therapy compared with MTX monotherapy (14). In this report, results are presented from the second year of the COMET trial, which determined how continuation of and alterations to the initial combination and monotherapy regimens affected long-term clinical and radiographic outcomes. A list of COMET investigators is shown in Appendix A.

**SUBJECTS AND METHODS**

**Subjects.** The COMET study design has been described previously in detail (14). All subjects who completed 1 year of treatment in the COMET study were eligible for enrollment in the second year of the study. At the baseline of year 1, subjects who had never received MTX and who had active RA with a disease duration of 3–24 months (early RA) were randomly assigned to 1 of 4 treatment groups, as follows: 1) combination etanercept plus MTX treatment in year 1 followed by continued combination treatment in year 2 (EM/EM), 2) combination treatment in year 1 followed by etanercept alone in year 2 (EM/E), 3) MTX monotherapy in year 1 followed by combination treatment in year 2 (M/M), or 4) MTX monotherapy in year 1 followed by continued MTX monotherapy in year 2 (M/M).

**Protocol.** Subjects were randomly assigned to a treatment group only once, at the baseline of the study, with no rerandomization occurring at the end of year 1. Treatment was allocated with a computerized randomization and enrollment system that masked both participants and investigators at original baseline and during the transition from year 1 to year 2. Investigators, study team members, and subjects remained blinded to treatment assignment until the end of year 2.

Participants received 50 mg etanercept by subcutaneous injection or placebo injection once weekly. Oral MTX or placebo was administered once weekly. In subjects receiving MTX or oral placebo in both study years, the same dosage was maintained; no reduction in MTX or oral placebo was permitted in year 2, except in the EM/E group. In that group, MTX was discontinued according to a prespecified blinded downward titration schedule over the first 4 weeks of year 2. Procedures related to usage of corticosteroids, nonsteroidal antiinflammatory drugs, and folic acid supplementation have been described previously (14). Administration of parenteral corticosteroids was permitted after week 52, with a limit of 1 injection every 8 weeks.

This study was done in accordance with the ethical principles of the Declaration of Helsinki. The protocol and its amendments received independent ethics committee or institutional review board approval and regulatory review and
approval before site initiation and recruitment of subjects. All elements of informed consent were explained to eligible subjects, and adequate time was allowed for questions and for subjects to make voluntary decisions. No subject underwent procedures specific to the protocol until he or she had signed and dated an approved informed consent form.

**End points.** The co–primary end points of the percentage of subjects with disease in remission according to the DAS28 and radiographic nonprogression at week 52 have been reported previously (14). For study year 2, clinical efficacy end points included the proportions of subjects in the 4 treatment groups achieving DAS28 remission at week 104, the proportions of subjects in the 4 treatment groups meeting the American College of Rheumatology 20% improvement criteria (achieving an ACR20 response) (15) or achieving an ACR50 or ACR70 response at week 104, and changes in the mean DAS28 and 28-swollen-joint count in the 4 treatment groups from week 52 to week 104.

Joint space narrowing and joint erosion were assessed, and the modified Sharp/van der Heijde score (SHS; range 0–448) (16–18) was calculated for all groups. Radiographic end points included the proportion of subjects achieving radiographic nonprogression at week 104 (change from week 52 in SHS ≤0.5 [18]) and the rate of change in the SHS from baseline to week 52 and from week 52 to week 104. Two separate physicians who were masked to the treatment regimen and sequence of films read the digitized radiographic images (BioImaging Technologies, Newtown, PA) for all participants in a randomized sequence (the interrater correlation was 0.935–0.961). Functional improvement was measured using the disability index of the Health Assessment Questionnaire (HAQ DI) (19), and the proportion of subjects in each group who achieved a normal HAQ DI score (≤0.5 [20,21]) was evaluated. A post hoc analysis of the proportions of subjects who achieved DAS28 remission, radiographic nonprogression, and a normal HAQ DI score was performed at week 104; subjects who had missing data at week 104 were considered to be nonresponders for this composite end point.

**Statistical analysis.** Power determinations for year 2 assumed 2-sided testing at the 0.05 significance level. Based on the expected percentages of subjects discontinuing participation in the study at 1 year of 20% in the combination therapy group and 30% in the MTX monotherapy group, 216 subjects (108 subjects in both the combination therapy and etanercept monotherapy groups) and 189 subjects (94–95 subjects in the combination and MTX monotherapy groups), respectively, were expected to enter year 2 of the study. On the assumption of a difference between the latter groups of 1.21 to 1.85 and an SD of 4.5, there was 80% power to detect a significant difference in the SHS change from week 52 to week 104.

Statistical comparisons for clinical and radiographic efficacy end points tested the null hypotheses that there were no differences between the EM/EM and EM/E groups, EM/EM and M/EM groups, EM/EM and M/M groups, and M/EM and M/M groups. The proportions of subjects achieving DAS28 remission and radiographic nonprogression were compared using Fisher’s exact test. The mean SHS changes from year 2 baseline (week 52) to week 104 were compared between treatment groups using analysis of covariance on the rank of the change scores, averaged over readers, with the rank of baseline scores as covariate.

The modified intention-to-treat (ITT) population for clinical efficacy analyses included all enrolled subjects who received at least 1 dose of the year 2 test article, for whom baseline DAS28 results were reported for year 2, and for whom DAS28 results while receiving therapy were reported at least once from week 52 to week 104. The radiographic modified ITT population included subjects who received at least 1 dose of year 2 test article and provided valid radiographs at baseline of year 1, at week 52 (baseline of the year 2 analysis), and at week 104 or early termination. For radiographic analyses, annualized progression rates were used for radiographs obtained before the week 104 visit. As prespecified for both clinical and radiographic analyses, missing values were imputed using the last observation carried forward (LOCF) method. A post hoc statistical analysis of DAS28 remission was subsequently performed using nonresponder imputation (NRI) at week 104, with subjects who discontinued at any point during the 2-year study counted as nonresponders. A post hoc observed analysis of the proportion of subjects who achieved a DAS28 <2.6, an HAQ DI score ≤0.5, and a change in the SHS ≤0.5 over the second year of the study was also performed on those subjects with year 2 radiographs. A number-needed-to-treat analysis, recommended in rheumatology (22), was conducted for DAS28 remission and radiographic nonprogression in the EM/EM group compared with the M/M group. Safety analyses included all subjects who entered year 1 and received at least 1 dose of year 1 test article (n = 542) and those subjects who continued into year 2 and received at least 1 dose of year 2 test article (n = 411).

**RESULTS**

A total of 411 subjects completed 1 year of either combination therapy or MTX monotherapy and continued into year 2 of this trial as originally randomized (Figure 1). Of these, 398 subjects were valid for evaluation of clinical efficacy, and all 411 subjects were valid for evaluation of safety. Overall, 64 subjects (15.6%) discontinued participation in the study from week 52 to week 104; subjects in the EM/EM treatment group were significantly less likely to discontinue treatment due to lack of efficacy than subjects in other treatment groups (P < 0.01). The mean weekly doses of MTX from week 52 to week 104 in the EM/EM, EM/E, M/EM, and M/M groups were 16.2 mg, 16.3 mg (MTX placebo), 17.8 mg, and 18.0 mg, respectively; the maximum allowable dosage was 20 mg/week, based on the standard of care at the time the protocol was written. A total of 360 subjects were included in the year 2 radiographic analysis (99 subjects in the EM/EM group, 99 in the EM/E group, 79 in the M/EM group, and 83 in the M/M group). Demographics and baseline disease characteristics are summarized in Table 1. In a post hoc NRI analysis over 104 weeks, 528 subjects were evaluated for DAS28 remission.

**Efficacy.** After 2 years of treatment (LOCF method), the proportions of subjects achieving DAS28 remission in the EM/EM and M/EM groups (62/108
and 51/88 [58%], respectively) were significantly greater than that in the M/M group (33/94 [35%]) (P/H11005 0.002 for EM/EM group versus M/M group; P/H11005 0.003 for M/EM group versus M/M group) but not significantly greater than that in the EM/E group (54/108 [50%]). Based on the NRI analysis, significantly greater proportions of subjects in the EM/EM (59/131 [45%]), EM/E (50/134 [37%]), and M/EM (48/133 [36%]) groups were similarly shown to have achieved DAS28 remission after 2 years compared with the M/M group (29/130 [22%]) (P/H11021 0.001 for EM/EM group versus M/M group; P/H11005 0.010 for EM/E group versus M/M group; P/H11005 0.015 for M/EM group versus M/M group). Worsening of the mean DAS28 was observed from weeks 52 to 104 in the EM/E group (from 2.6 to 3.1; P < 0.05 versus the EM/E group), and minimal change was seen in the M/M group (from 3.4 to 3.5).

The percentages of subjects in the EM/EM, EM/E, M/EM, and M/M groups who achieved an ACR20 response at week 104 were 86%, 80%, 81%, and 61%, respectively. Statistically significant differences were noted at week 104 in the M/EM group compared with the M/M group (P/H11005 0.004) and in the EM/EM group compared with the M/M group (P < 0.001). For the ACR50 response, the percentages of responders in the EM/EM, EM/E, M/EM, and M/M groups were 70%, 64%, 66%, and 46%, respectively. Statistically significant differences were found in the M/EM group compared with the M/M group (P = 0.007) and in the EM/E group compared with the M/M group (P < 0.001). An ACR70 response was achieved in 57%, 44%, 48%, and 32% of the EM/EM, EM/E, M/EM, and M/M groups, respectively, with statistically significant differences be-

![Figure 1. Study design and subject disposition. EM/EM = combination etanercept plus methotrexate (MTX) treatment in year 1 followed by continued combination treatment in year 2; EM/E = combination treatment in year 1 followed by etanercept alone in year 2; M/EM = MTX monotherapy in year 1 followed by combination treatment in year 2; M/M = MTX monotherapy in year 1 followed by continued MTX monotherapy in year 2. * = 1 subject discontinued at final visit of year 1 but received 1 dose of study drug in period 2 (included in period 2 population); † = overall P = 0.003, by 2-tailed Fisher’s exact test.](image-url)
between the M/EM and the M/M groups (P = 0.034) and between the EM/EM and the M/M groups (P < 0.001).

During year 2, radiographic nonprogression (LOCF method; SHS ≤0.5) was demonstrated in a significantly higher proportion of subjects in the EM/EM group (89/99 [90%]) than in the EM/E (74/99 [75%]), M/EM (59/79 [75%]), and M/M (56/83 [67%]) groups (P = 0.008 for the EM/EM group versus the EM/E group; P = 0.009 for the EM/EM group versus the M/EM group; P < 0.001 for the EM/EM group versus the M/M group) (Figure 3). The estimated number of persons who would need to be treated with the EM/EM regimen rather than the M/M regimen for 2 years to achieve radiographic nonprogression was 4.5 (95% CI 2.8, 10.4). The mean SHS changes from week 52 to week 104 were −0.02 (95% CI −0.32, 0.29), 0.11 (95% CI −0.54, 0.77), 0.78 (95% CI −0.06, 1.61), and 2.07 (95% CI 0.42, 3.72) for the EM/EM, EM/E, M/EM, and M/M groups, respectively; the change in the EM/EM group was significantly less than the change in the EM/E group (P = 0.006). From week 52 to week 104, improvements from 1.7 to 1.3 and from 2.6 to 1.3 were achieved in the mean 28-swollen-joint counts in the EM/EM and M/EM groups, respectively, compared with worsening from 1.1 to 1.7 and from 2.4 to 2.9 in the EM/E and M/M groups, respectively (P = 0.001 for the M/EM group versus the M/M group).

The proportions of subjects achieving normal HAQ DI scores at week 52 differed significantly between the EM/EM and M/M groups (57% and 43%, respectively; P = 0.048). The addition of etanercept to MTX produced significant within-group improvement in the raw mean score for change from week 52 to week

Table 1. Demographics at the year 1 baseline and disease characteristics at the year 2 baseline for the year 2 modified intention-to-treat population*

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>EM/EM (n = 108)</th>
<th>EM/E (n = 108)</th>
<th>M/EM (n = 88)</th>
<th>M/M (n = 94)</th>
<th>Total (n = 398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>52.4 ± 14.3</td>
<td>52.2 ± 14.6</td>
<td>55.6 ± 13.1</td>
<td>53.2 ± 12.5</td>
<td>53.2 ± 13.7</td>
</tr>
<tr>
<td>Women, no. (%)</td>
<td>78 (72.2)</td>
<td>82 (75.9)</td>
<td>52 (59.1)</td>
<td>77 (81.9)</td>
<td>289 (72.6)</td>
</tr>
<tr>
<td>White, no. (%)</td>
<td>94 (87.0)</td>
<td>95 (88.0)</td>
<td>78 (88.6)</td>
<td>83 (88.3)</td>
<td>350 (87.9)</td>
</tr>
<tr>
<td>Disease duration, months</td>
<td>8.4 ± 5.7</td>
<td>9.1 ± 5.6</td>
<td>9.1 ± 6.0</td>
<td>8.7 ± 5.4</td>
<td>8.8 ± 5.7</td>
</tr>
<tr>
<td>DAS28</td>
<td>2.7 ± 1.2</td>
<td>2.6 ± 1.2</td>
<td>3.3 ± 1.4</td>
<td>3.4 ± 1.4</td>
<td>3.0 ± 1.4</td>
</tr>
<tr>
<td>Swollen joint count, 0–68</td>
<td>2.7 ± 6.1</td>
<td>1.5 ± 3.1</td>
<td>3.9 ± 6.4</td>
<td>3.1 ± 4.4</td>
<td>2.7 ± 5.2</td>
</tr>
<tr>
<td>Tender joint count, 0–71</td>
<td>3.9 ± 7.3</td>
<td>3.7 ± 7.9</td>
<td>6.5 ± 10.2</td>
<td>6.1 ± 7.9</td>
<td>4.9 ± 8.4</td>
</tr>
<tr>
<td>ESR, mm/hour</td>
<td>15.8 ± 12.4</td>
<td>15.3 ± 12.8</td>
<td>22.5 ± 15.9</td>
<td>22.7 ± 17.8</td>
<td>18.8 ± 15.1</td>
</tr>
<tr>
<td>Anti-CCP positive, no. (%)</td>
<td>72 (67.3)</td>
<td>74 (68.5)</td>
<td>63 (72.6)</td>
<td>64 (69.6)</td>
<td>273 (69.1)</td>
</tr>
<tr>
<td>CRP level, mg/liter</td>
<td>6.0 ± 5.0</td>
<td>7.6 ± 13.9</td>
<td>10.0 ± 13.8</td>
<td>10.5 ± 14.6</td>
<td>8.3 ± 12.4</td>
</tr>
</tbody>
</table>

*Except where indicated otherwise, values are the mean ± SD. EM/EM = combination etanercept plus methotrexate (MTX) treatment in year 1 followed by continued combination treatment in year 2; EM/E = combination treatment in year 1 followed by etanercept alone in year 2; M/EM = MTX monotherapy in year 1 followed by combination treatment in year 2; M/M = MTX monotherapy in year 1 followed by continued MTX monotherapy in year 2; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; anti-CCP = anti-cyclic citrullinated peptide; CRP = C-reactive protein.
### Table 2. Safety summary in the year 1 and year 2 safety populations*

<table>
<thead>
<tr>
<th>Event</th>
<th>Year 1 treatment group</th>
<th>Year 2 treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EM (n = 274)</td>
<td>M (n = 268)</td>
</tr>
<tr>
<td>Any treatment-emergent adverse event</td>
<td>246 (89.8)</td>
<td>241 (89.9)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>33 (12.0)</td>
<td>34 (12.7)</td>
</tr>
<tr>
<td>Death‡</td>
<td>1 (&lt;0.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Malignancy‡</td>
<td>4 (1.5)</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Serious infection</td>
<td>5 (1.8)</td>
<td>8 (3.0)</td>
</tr>
<tr>
<td></td>
<td>EM/EM (n = 111)</td>
<td>EM/E (n = 111)</td>
</tr>
<tr>
<td>Any treatment-emergent adverse event</td>
<td>91 (82.0)</td>
<td>89 (80.2)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>8 (7.2)</td>
<td>10 (9.0)</td>
</tr>
<tr>
<td>Death‡</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Malignancy‡</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Serious infection</td>
<td>1 (0.9)</td>
<td>2 (1.8)</td>
</tr>
</tbody>
</table>

* Values are the number (%) of subjects. EM = combination etanercept plus methotrexate (MTX) treatment; M = MTX monotherapy (see Table 1 for other definitions).

† One subject in the EM/E group died of pneumonia during year 1. One subject in the M/M group died during year 2; pneumonia and adenocarcinoma of the lungs with metastasis were reported as the cause of death.

‡ Nine malignancies were reported: 1 case each of gastrointestinal cancer, bladder cancer, rectal melanoma with metastasis to the lung, and prostate cancer in the M/EM group; 1 case each of pancreatic cancer and cancer of the chest wall and lungs in the M/M group; 1 case of basal cell cancer in each of the EM/E, M/EM, and M/M groups.

104 (mean ± SD change 0.17 ± 0.42) (P = 0.0007); mean changes in scores for the other treatment groups did not reach statistical significance. Comparing the proportions of subjects with normal HAQ DI scores, statistically significant differences were noted at week 104 only between the EM/EM and M/M groups (62% and 44%, respectively; P = 0.011).

A post hoc completers’ analysis of the proportions of subjects who achieved DAS28 remission (DAS28 <2.6), radiographic nonprogression (change in the SHS ≤0.5 from week 52 to week 104), and a normal HAQ DI score (≤0.5) at week 104 demonstrated a trend toward higher percentages of responders in the groups that included etanercept in the therapy regimen during year 2. Thirty-nine percent of the EM/EM group, 32% of the EM/E group, and 36% of the M/EM group achieved all 3 responses, while only 18% of the M/M group achieved this composite outcome.

**Safety.** During this 2-year study, combination therapy was well tolerated, with no new safety signals identified and no significant differences among groups (Table 2). No cases of opportunistic infection, tuberculosis, or demyelinating diseases were reported.

## DISCUSSION

In recent years, the use of MTX and combination DMARD therapy for RA has begun to address the underlying joint destruction that resulted in deformities and disability. However, new research suggests that radiographic progression may continue in patients receiving treatment, even when clinical remission is achieved (7–9). The most robust evidence of joint damage prevention is derived from clinical trials of anti-TNF agents, which have been shown to be particularly effective when used in combination with high-dose MTX in RA (23–25). This is especially the case for early RA (26–28), which is important because studies have demonstrated a rapid progression of radiographic damage in the first few years of disease (29–33), potentially representing the beginning of a lifetime of cumulative destruction. A “therapeutic window of opportunity” has been proposed in which treatment administered early may modify the underlying disease processes, halt the destruction of joints, and prevent a base level of joint damage (34–37).

To begin to explore this possibility, subjects with early RA in the first year of the COMET study were treated with combination therapy or MTX alone. At 1 year, the percentage of subjects in the combination group achieving DAS28 remission was nearly twice that in the MTX monotherapy group (50% versus 28%; P < 0.0001), and the percentage of subjects with no radiographic progression was also considerably higher (80% versus 59%; P < 0.0001) (14). The second year of the COMET study determined whether these important effects of combination therapy could be maintained compared with MTX monotherapy without sacrificing safety.

Sustained combination therapy was consistently more effective than continuous MTX monotherapy in improving clinical and radiographic outcomes. This was reflected in the greater numbers of subjects who withdrew from the M/M group due to lack of efficacy, both in year 1 (9 in the EM group versus 24 in the M group; P = 0.007) and in year 2 (none in the EM/EM group versus 7 in the M/M group; P = 0.003). The EM/EM regimen was associated with significantly higher rates of DAS28 remission, ACR response, and SHS nonprogres-
sion than was the M/M regimen. Importantly, the M/M group had a mean progression of 2.07 SHS units compared with a decrease of -0.02 for combination therapy (EM/EM)–treated subjects during year 2. This represents continued underlying joint destruction in the M/M group as opposed to the EM/EM group.

The second year of this study also evaluated the effect of switching to combination therapy after 1 year of MTX monotherapy switching to the M/EM regimen were significantly more effective than continuing MTX monotherapy (the M/M regimen) in providing DAS28 remission. Similar percentages of subjects in the M/EM and EM/EM groups achieved DAS28 remission at 2 years (58% and 57%, respectively; \( P \) not significant [NS]), according to the LOCF analysis. A more conservative post hoc 2-year NRI analysis, which accounted for the greater number of dropouts in the MTX treatment arm during year 1, revealed a numerically higher percentage of subjects with disease in remission in the EM/EM group than in the M/EM group (45% versus 36%; \( P \) NS). Furthermore, delaying combination therapy until year 2 of the study resulted in a significantly lower percentage of subjects attaining radiographic nonprogression compared with early and sustained combination therapy (75% versus 90%; \( P = 0.009 \)). These findings suggest that delaying the addition of etanercept to an MTX regimen for 1 year creates a potential “trade off.” Although, on a group level, the cost of deferred combination therapy is lower compared with that of early combination therapy, this delay may result in failure to achieve clinical remission and in residual radiographic damage.

We also assessed the effects of a step down from the EM regimen in year 1 to the EM/E regimen in year 2. This regimen was numerically less effective than continuous combination therapy in providing DAS28 remission (50% versus 57%; \( P \) NS) and significantly less effective in producing nonprogression (75% versus 90%; \( P = 0.008 \)).

Outcomes at year 2 (LOCF method) in the EM/E group were numerically, but not statistically, superior to those in the M/M group in terms of both DAS28 remission (50% versus 35%; \( P \) NS) and radiographic nonprogression (75% versus 68%; \( P \) NS), demonstrating the importance of MTX as an adjunct to etanercept for optimizing clinical and radiographic outcomes in early RA. Nevertheless, the efficacy of the step-down approach may be an encouraging finding for patients who do not tolerate MTX or otherwise need to discontinue treatment with this agent. It is of note that none of the 111 subjects who had received combination therapy for the full 2 years of the study and only 1 of 90 who switched to combination therapy for the second year dropped out due to lack of efficacy compared with 7 of the 99 subjects who had received MTX monotherapy for 2 years and 7 of 111 who continued receiving etanercept only in the second year. On NRI analysis, both the M/EM and EM/E therapy regimens led to similar DAS28 responses.

The addition of etanercept to MTX at week 52 altered the rate of change in SHS, so that the continued progression over the second year of the study more closely resembled that of the EM/E group. However, the total SHS for the M/M group was observed to be greater than that of the EM/E group at week 104, due to the residual radiographic damage from year 1 (Figure 4). This again suggests that the early use of combination therapy protects against joint damage and subsequent loss of function over time. Additionally, the initial year of combination therapy appeared to support achievement of the composite outcome of DAS28 remission, radiographic nonprogression, and a normal HAQ DI score. In the EM/EM, EM/E, and M/EM groups, the proportions of subjects who achieved all 3 results (39%, 32%, and 36%, respectively) approximated the rate of this response seen in the first year of the COMET trial (35%) (14), while the proportion in the M/M group (18%) was considerably lower.

The results of this trial further address whether the benefits of combination therapy in early RA outweigh the potential side effects of long-term administration. Combination therapy continued to be well tolerated over the second year of observation, with no new safety signals reported during year 2, suggesting that early and sustained intensive therapy can improve long-term outcomes for subjects with early RA without posing an additional safety risk.

This study had several limitations, which included...
potential distribution disparities since the 2-year end points were reported only for those subjects who completed year 1 of the study and did not account for the greater number of discontinuations in the M/M group in year 1. Randomization to the year 2 treatment groups occurred at study entry (baseline of year 1); hence, not all subjects randomized to year 2 groups were present in the year 2 efficacy population, due to withdrawals during year 1. For these reasons, an NRI analysis was performed. In contrast to subjects treated in clinical practice, COMET participants were not permitted to reduce the dosage of their primary medication unless required due to adverse events, which does not reflect current practice. Furthermore, the 20-mg maximal dose of MTX might not be considered sufficiently aggressive by some clinicians today, although this was the state of the art when the COMET study was designed. Modifications in MTX dosages (either up or down) or other therapeutic interventions based on clinical response or DAS28 might have yielded different outcomes. Also, treatment group means were analyzed in this study, so these results need to be interpreted with caution when considering individual patients. Finally, for purposes of simplicity, this study did not have a fifth step-down treatment arm in which etanercept was discontinued following the combination EM regimen in year 1. The results of this study, however, have generated interest in further exploring etanercept step-down therapy regimens for patients who achieve remission of disease with combination therapy, with the possibility of drug-free remission as a goal for some RA patients.

In conclusion, the final results of the COMET trial underscore a growing body of evidence that demonstrates the important sustained clinical benefits of intensive therapy in early RA. Combination therapy with etanercept and MTX led to DAS28 remission in approximately half of the subjects at year 2, with 90% of subjects showing no radiographic progression. Even though 3 alternative regimens led to good responses compared with those achieved with treatment in past decades, the combination regimen for 2 years appeared to produce the optimal results with no compromise in safety.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Emery had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. Emery.

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REFERENCES


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