Continuation of Methotrexate Resulted in Better Clinical and Radiographic Outcomes Than Discontinuation upon Starting Etanercept in Patients with Rheumatoid Arthritis: 52-week Results from the JESMR Study

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ABSTRACT. Objective. The aim of the Efficacy and Safety of Etanercept on Active Rheumatoid Arthritis Despite Methotrexate Therapy in Japan (JESMR) study is to compare the efficacy of continuation versus discontinuation of methotrexate (MTX) when starting etanercept (ETN) in patients with active rheumatoid arthritis (RA).

Methods. In total, 151 patients with active RA who had been taking MTX were randomized to either ETN 25 mg twice a week with 6–8 mg/week MTX (the E+M group), or ETN alone (the E group). The primary endpoint at Week 52 was the radiographic progression assessed by van der Heijde-modified Sharp score.

Results. The mean progression in total score at Week 52 was not significantly different, statistically, between the E+M group and the E group (0.8 vs 3.6, respectively; p = 0.06). However, a significant difference was observed in radiographic progression between Weeks 24 and 52 (0.3 vs 2.5; p = 0.03), and the mean progression of the erosion score was negative in the E+M group, which was significantly better than the E group at Week 52 (~0.2 vs 1.8; p = 0.02). Clinically, the cumulative probability plot of the American College of Rheumatology (ACR)-N values at Week 52 clearly demonstrated a superior response in the E+M group than in the E group. ACR20, 50, and 70 response rates at Week 52 in the E+M group (86.3%, 76.7%, and 50.7%) were significantly greater than those in the E group (63.8%; p = 0.003, 43.5%; p < 0.0001 and 29.0%; p = 0.01, respectively).

Conclusion. MTX should be continued when starting ETN in patients with active RA.

Key Indexing Terms: METHOTREXATE, RHEUMATOID ARTHRITIS, TNFR-Fc FUSION PROTEIN
The introduction of biological agents such as tumor necrosis factor-α (TNF-α) inhibitors into the therapeutic strategy for rheumatoid arthritis (RA) resulted in a shift characterized by the sufficient inhibition of arthritic signs and symptoms, radiographic progression, and functional disability. However, the optimal use of those agents remains to be determined. For example, etanercept (ETN) has been shown to be effective for RA both as a monotherapy and as combination therapy with methotrexate (MTX), and the latter has proved its superiority to the former in MTX-naive patients. Because MTX is the first-line drug for most patients with RA, and ETN is much more expensive than MTX, ETN tends to be started for MTX-refractory, but not MTX-naive, patients in actual clinical practice.

The Add Enbrel or Replace Methotrexate (ADORE) trial was the first to consider whether adding ETN to MTX is better than replacing MTX with ETN. The trial failed to demonstrate the superiority of continuing MTX rather than discontinuing it upon starting ETN therapy. Because the ADORE trial was only 16 weeks, with a regimen of MTX tapering over the initial 4 weeks, there could be no marked difference between continuation versus discontinuation of MTX, if any difference at all. Longterm efficacy and safety was not compared between the 2 groups.

Therefore, we conducted the Efficacy and Safety of Etanercept on Active Rheumatoid Arthritis Despite Methotrexate Therapy in Japan (JESMR) study to address the differences in clinical activity, radiographic progression, and functional disability over 2 years. The 24-week results from the JESMR study demonstrated that continuation of MTX after the start of ETN was better than discontinuation of MTX, in terms of European League Against Rheumatism (EULAR) response and American College of Rheumatology (ACR20) response rates. We report the 52-week results, focusing on the radiographic progression measured by van der Heijde-modified Sharp (vdH-Sharp) score (which had been included in the co-primary endpoint), the ACR response, and functional disability evaluated by the Health Assessment Questionnaire-Disability Index (HAQ-DI).

**RESULTS**

Primary endpoint: radiographic efficacy. Efficacy analysis was performed in 69 patients of the E group and 73 of the E+M group (Figure 1). The rate of per-protocol patients was smaller in the E group than in the E+M group, chiefly because of a lack of efficacy after 24 weeks.

The baseline vdh-Sharp score was 114.5 ± 85.7 in the E group and 113.1 ± 85.6 in the E+M group (p = 0.99). Cumulative probability plot analysis suggested less overall radiographic progression in the E+M group than in the E group during the 52 weeks (Figure 2A). However, the primary endpoint at 52 weeks was not met because the numerical superiority of the E+M group over the E group in the change in vdh-Sharp score over 52 weeks did not reach a statistically significant difference (0.8 vs 3.6, respectively; p = 0.06), as shown in Figure 2B. Nonetheless, the mean progression in the erosion score was negative exclusively in the E+M group, at
both 24 weeks and 52 weeks (–0.1 and –0.2, respectively), and it was significantly better than that in the E group at 52 weeks (1.8; p = 0.02). Moreover, a significant difference was observed in the total score progression between Weeks 24 and 52 (2.5 in the E group and 0.3 in the E+M group; p = 0.03), suggesting the carrying-over effect of MTX for the initial few months.

The proportion of patients showing no radiographic progression over 52 weeks (change in vdH-Sharp score ≤ 0.5) was 39.6% in the E group and 57.4% in the E+M group (p = 0.07), and the proportion showing no clinically significant radiographic progression (change in vdH-Sharp score ≤ smallest detectable change) was 58.5% in the E group and 67.6% in the E+M group (p = 0.34).

Clinical efficacy. Next we performed for the first time a cumulative probability plot analysis of ACR-N values at 52 weeks for both treatment groups (Figure 3). This analysis clearly demonstrated the superior clinical response in the E+M group compared to the E group, and implied that the continuation of MTX would be beneficial, at least to some extent, in nearly 80% of patients upon the commencement of ETN. Indeed, the mean ± SD of ACR-N was 60.9 ± 29.3 for the E+M group, which was significantly greater than that of the E group (31.1 ± 50.8; p = 0.0003). In addition, the area under the curve of the ACR-N throughout 52 weeks was also significantly different between the groups (26.8 ± 13.0 in the E+M group and 18.4 ± 19.0 in the E group; p = 0.008). At the same time, we could easily see the superior ACR response rates in the E+M

Table 1. Demographic features of the patients. Except where indicated otherwise, values are mean ± SD.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ETN, n = 71</th>
<th>ETN + MTX, n = 76</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>58.1 ± 12.6</td>
<td>56.6 ± 11.1</td>
<td>0.23</td>
</tr>
<tr>
<td>Women, %</td>
<td>87.3</td>
<td>80.3</td>
<td>0.27</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>51.0 ± 8.4</td>
<td>54.6 ± 11.3</td>
<td>0.057</td>
</tr>
<tr>
<td>Disease duration, yrs</td>
<td>10.6 ± 10.5</td>
<td>8.0 ± 7.6</td>
<td>0.21</td>
</tr>
<tr>
<td>Positive rheumatoid factor, %</td>
<td>91.5</td>
<td>86.7</td>
<td>0.43</td>
</tr>
<tr>
<td>MTX dose, mg/wk</td>
<td>7.0 ± 1.4</td>
<td>7.4 ± 1.1</td>
<td>0.099</td>
</tr>
<tr>
<td>Total vdH-Sharp score, (median; IQR)</td>
<td>114.5 ± 85.7 (94.5; 120.0)</td>
<td>113.1 ± 85.6 (89.5; 91.0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Estimated yearly progression, (median; IQR)</td>
<td>17.7 ± 13.2 (13.9; 16.0)</td>
<td>20.8 ± 18.2 (4.4; 12.2)</td>
<td>0.45</td>
</tr>
<tr>
<td>Erosion score, (median; IQR)</td>
<td>55.6 ± 53.0 (43.5; 59.5)</td>
<td>56.6 ± 54.4 (37.8; 53.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>Joint space narrowing score, (median; IQR)</td>
<td>58.9 ± 33.9 (54.0; 55.0)</td>
<td>56.5 ± 32.9 (47.8; 41.4)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

ETN: etanercept; MTX: methotrexate; vdH: van der Heijde; IQR: interquartile range.

Figure 1. Disposition of patients during 52 weeks of the Efficacy and Safety of Etanercept on Active Rheumatoid Arthritis Despite Methotrexate Therapy in Japan (JESMR) study. A total of 151 patients were enrolled, 74 in the etanercept (ETN) group and 77 in the etanercept and methotrexate (MTX) group, and 108 patients (71.5%) completed 52 weeks per protocol.
Figure 2. Change in van der Heijde-modified Sharp (vdH-Sharp) total score represented by cumulative probability plot (A) and the mean change of total score as well as erosion and joint space narrowing scores (B) over 52 weeks. Values are mean ± SEM, compared by Mann-Whitney U test (*p = 0.03; **p = 0.02) between groups. ETN: etanercept group; ETN+MTX: etanercept plus methotrexate group.
group compared to the E group, as shown in Figure 3: 86.3% vs 63.8% in ACR20 (p = 0.003), 76.7% vs 43.5% in ACR50 (p < 0.0001), and 50.7% vs 29.0% in ACR70 (p = 0.01), respectively (Table 2). Except for patient global assessment, all important clinical measures, including HAQ-DI, favored the continuation of MTX at Week 52, as shown in Table 2.

Safety analyses. Safety profiles between the 2 treatment groups were comparable (Table 3). Similar overall adverse events were observed between the treatment groups. The frequency of general disorders and administration site conditions, mostly injection site reaction (13 in the E group and 7 in the E+M group), tended to be higher in the E group than the E+M group, as well as skin and subcutaneous tissue disorders including eczema and erythema developed at sites unrelated

Table 2. Comparison of the clinical responses between treatment groups. Except where indicated otherwise, values are mean ± SD.

<table>
<thead>
<tr>
<th>Measures</th>
<th>ETN, n = 69</th>
<th>MTX + ETN, n = 73</th>
<th>p at 52 Weeks Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender joint count (68 assessed)</td>
<td>15.0 ± 9.4</td>
<td>15.1 ± 8.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Swollen joint count (66 assessed)</td>
<td>12.4 ± 6.1</td>
<td>12.5 ± 6.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Patient global assessment</td>
<td>62.5 ± 20.5</td>
<td>53.7 ± 23.7*</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>ESR, mm/l h</td>
<td>59.7 ± 28.4</td>
<td>59.5 ± 26.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>2.5 ± 2.5</td>
<td>3.0 ± 3.2</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>DAS28</td>
<td>6.1 ± 0.9</td>
<td>6.0 ± 1.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>EULAR good response, %</td>
<td>—</td>
<td>52.1</td>
<td>—</td>
</tr>
<tr>
<td>DAS28 &lt; 2.6, %</td>
<td>0</td>
<td>35.6</td>
<td>—</td>
</tr>
<tr>
<td>ACR20 responder, %</td>
<td>—</td>
<td>86.3</td>
<td>—</td>
</tr>
<tr>
<td>ACR50 responder, %</td>
<td>—</td>
<td>76.7</td>
<td>—</td>
</tr>
<tr>
<td>ACR70 responder, %</td>
<td>—</td>
<td>50.7</td>
<td>—</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>1.3 ± 0.8</td>
<td>1.2 ± 0.7</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

* A significant difference between groups was observed at Week 0 (about 4 weeks after enrollment shown in Table 1) for patient’s global assessment value, in which p value was 0.025. ETN: etanercept; MTX: methotrexate; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28: 28-joint Disease Activity Score; EULAR: European League Against Rheumatism; ACR: American College of Rheumatology; HAQ-DI: Health Assessment Questionnaire-Disability Index.
to ETN injection. In contrast, the frequency of hepatobiliary disorders, mostly liver dysfunction, tended to be higher in the E+M group than in the E group. The result was the same between the groups with metabolism and nutrition disorders such as hyperlipidemia, diabetes mellitus, and hyperuricemia. Serious adverse events in the E group were bone fractures in 2 patients (humeral bone and osteoporotic vertebrae). Serious adverse events in the E+M group were bone fractures in 3 (femoral bone in 2, cranial bone in 1), and in 1 patient each, congestive heart failure, cellulitis, herpes zoster, brain hemorrhage, and mammary carcinoma. Cranial bone fracture from a traffic accident and cellulitis developed in the same patient. Treatment was withdrawn because of injection site reaction in 4 patients in the E group and mammary carcinoma in 1 patient in the E+M group. Thus, the safety profile was comparable between 2 groups.

DISCUSSION

In a previous report on the 24-week results of the JESMR study, the superiority of a continuation of MTX over its discontinuation when starting ETN in terms of controlling clinical disease activity (the rates of EULAR good response, remission, and ACR20 response, but not ACR50 and 70 responses) was indicated6. Our 52-week results not only confirmed the previous ones but also proved, for the first time, that the combination of ETN and MTX resulted in a better outcome in radiographic progression determined by vdH-Sharp score, especially in erosions, even in patients who had shown an incomplete response to MTX. The mean progression in total score at Week 52 was not significantly different, statistically, between the E+M group and the E group (0.8 vs 3.6, respectively; p = 0.06). The chief reason for failure to achieve the primary endpoint seemed to be the reduction in sample size due to delayed recruitment of patients. However, a significant difference was observed in radiographic progression between Weeks 24 and 52 (0.3 vs 2.5, respectively; p = 0.03), and the mean progression of the erosion score was negative in the E+M group, which was significantly better than the E group at Week 52 (~0.2 vs 1.8, respectively; p = 0.02). Further, all important clinical measures, including ACR responses, EULAR responses, and HAQ-DI, favored the continuation of MTX at Week 52.

Infliximab was the first biological agent to have demonstrated complete inhibition of radiographic progression in combination with MTX in MTX-refractory patients with active RA11. ETN and adalimumab showed similar efficacy in halting joint destruction in combination with MTX. Both agents proved their superior clinical and radiographic efficacy with MTX combination over monotherapy in MTX-naive patients with early RA (the PREMIER study12) or established RA (the TEMPO study13). Our results led to the conclusion that anti-TNF biological agents should be used in combination with MTX as far as possible, whether the patients are MTX-naive or MTX-refractory, and they strongly support the recent recommendations of the ACR3 and EULAR4.

The reason that the continuation of MTX, which had only shown an inadequate response in the enrolled patients, demonstrated a significant effect with ETN treatment may be as follows: (1) the efficacy of MTX was insufficient but not negligible even as a monotherapy; and (2) the targets of MTX, including activated T cells14, are not identical to those of ETN, resulting in additive or synergistic effects between MTX and ETN. A recent report from the GO-FORWARD study also
demonstrated a better clinical response to golimumab with MTX continuation than with its discontinuation in MTX-refractory patients with RA. The fact that many clinical (ACR50 and 70 response rates and HAQ-DI score) and radiographic (erosion score progression) measures showed statistically significant differences at Week 52 but not at Week 24 may explain why the ADORE study did not show a difference between MTX continuation and discontinuation. The usefulness of MTX continuation seems to be true with all biological agents targeting TNF.

The average disease duration of about 9 years significantly affected the radiographic and HAQ-DI results in the JESMR study. Despite a long disease duration, our patients showed a rapid progression in vH-Sharp scores with a mean estimated yearly progression of 18–21 (Table 1). This result was close to that of patients with early active RA who were enrolled in the PREMIER study (26–27) and was much higher than that in the TEMPO study (8–11). This fact may explain, at least in part, the similarities and differences in the radiographic progression results among those clinical trials. In addition, the radiographic progression in our patients could be more aggressive in the initial few years after disease onset. Therefore, whether our results are also true for patients with early RA of < 6 months’ duration should be examined in the near future.

Most of the adverse events, including infections and skin disorders other than injection site reactions, were observed throughout 52 weeks. However, as expected, injection site reaction was less frequent after 24 weeks when compared to our previous report. In contrast, most of the bone fractures, which were the predominant serious adverse events in our study, developed after 24 weeks. This could be attributed at least in part to the improved activity of daily life of our patients treated with ETN as demonstrated by the HAQ-DI improvement (Table 2).

Our study has several limitations. First, it was not double-blinded. Therefore, one may assume there was an awareness of the treatment effect evaluations by physicians and by patients. However, the changes in acute-phase reactants (Table 2) and radiographic results (Figures 2A and 2B) make that unlikely. Further, there were considerable withdrawal rates in the E group (Figure 1), mostly because of a lack of efficacy after 24 weeks. Since this had been expected, because this study was not double-blinded, we applied the LOCF methods for clinical efficacy analyses instead of intention-to-treat analyses. In addition, the sample size of the JESMR study limited the power of detection of differences in both treatment groups. Finally, the dose of MTX approved by the Japanese Ministry of Health, Labor and Welfare had been only 6–8 mg/week throughout this study although, concordantly, the use of supplementary folic acid was also limited to about half of the patients receiving MTX. In February 2011, the Ministry approved MTX use up to 16 mg/week for patients with RA. Nonetheless, overall clinical and radiographic outcomes of infliximab added to MTX 7–9 mg/week in Japan were comparable to those in the ATTRACT and ASPIRE studies.

Future studies may also include the prediction of patient outcome after the start of ETN therapy, addressing the question of who can be sufficiently controlled by simply switching from MTX to ETN, and who can be sufficiently controlled by the addition of ETN to MTX but not by switching from MTX to ETN. These subanalyses are now under investigation in the Japan Biological Agent Integrated Consortium (J BASIC) study group.

Our results demonstrated for the first time that the continuation of MTX resulted in a better clinical and radiographic outcome, at least in some aspects, than its discontinuation after the start of ETN in patients with active RA despite MTX therapy. We also showed the usefulness of cumulative probability plot presentation not only for radiographic progression but also for clinical responses such as ACR-N, which may be included in future clinical trials.

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