Improvements in clinical response between 12 and 24 weeks in patients with rheumatoid arthritis on etanercept therapy with or without methotrexate

A Kavanaugh, L Klareskog, D van der Heijde, J Li, B Freundlich, M Hooper

ABSTRACT

Background: Whereas many patients respond quickly to treatment with tumour necrosis factor (TNF) inhibitors, some patients may experience significant but delayed responses. Objective: To evaluate the clinical response between 12 and 24 weeks in subjects with rheumatoid arthritis from the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes.

Methods: Clinical response was assessed at 24 weeks in 12-week non-responders, according to American College of Rheumatology (ACR) response criteria. The proportion of subjects who successfully maintained response to 52 weeks was analysed, as were radiographic outcomes.

Results: Data from 682 subjects were included in the analysis. Non and partial responders in all three groups (etanercept, methotrexate and etanercept plus methotrexate) at week 12 showed an improvement in responses at week 24. Over 80% of the week 24 ACR20/50/70 responders in the etanercept plus methotrexate arm sustained their response to 52 weeks. In the etanercept arms, a delayed clinical response was not associated with increased radiographic progression at week 52.

Conclusion: A significant proportion of non and partial responders to etanercept with or without methotrexate therapy at week 12 achieved a good clinical response or improved their overall clinical response at week 24. Discontinuing TNF inhibitor therapy at 12 weeks may be premature in some rheumatoid arthritis patients.
ment group. Bonferroni adjustment was used for multiple comparisons. Logistic regression models were used to identify predictors of response at 12 weeks. Results were considered significant at $p < 0.05$ two-sided. Non-responder imputation was used to handle missing clinical and radiographic data. All analyses were performed using the SAS STAT system version 9.1.

RESULTS
Baseline demographics
The TEMPO trial included 682 subjects (231 in the etanercept plus methotrexate arm, 223 in the etanercept monotherapy arm and 228 in the methotrexate monotherapy arm). Baseline demographic characteristics for TEMPO subjects have been described previously. Briefly, the mean disease duration was 6.8 years, with 76% of subjects rheumatoid factor positive. The mean age was 52.5 years and approximately three-quarters were women. Subjects had a mean baseline DAS28 score of 6.8.

Improvement in ACR response
Results from the analysis of ACR20/50/70 responses at week 24 in week 12 non and partial responders are shown in fig 1. In the etanercept plus methotrexate-treated subjects, 37.5% of week 12 ACR20 non-responders became ACR20 responders, 46.8% of week 12 ACR50 non-responders became ACR50 responders and 51.1% of week 12 ACR70 non-responders became ACR70 responders. Similar improvements were also observed in the monotherapy arms (23%–35% in the etanercept monotherapy arm and 41%–45% in the methotrexate monotherapy arm).

Sustainability of ACR response
Of 21 ACR20, 37 ACR50 and 23 ACR70 responders at week 24 in the etanercept plus methotrexate arm, 17 (81.0%), 31 (83.8%) and 19 (82.6%) subjects, respectively, showed a sustained response at week 24 (fig 1). The sustainability of response was more variable in the etanercept and methotrexate monotherapy arms, ranging from 67% to 89% and 50% to 63%, respectively.

A decrease in ACR20/50/70 response was observed in some subjects between weeks 12 and 24. In the etanercept plus methotrexate arm, 18 out of 175 ACR20 responders (10.3%), five out of 96 ACR50 responders (5.2%) and five out of 51 ACR70 responders (9.8%) decreased their response at week 24 (data not shown). Similarly, 11.5% of ACR20, 23.3% of ACR50 and 4.8% of ACR70 responders in the etanercept monotherapy arm and 16.5% of ACR20, 10.2% of ACR50 and 23.1% of ACR70 responders in the methotrexate monotherapy arm decreased their response between weeks 12 and 24.

Improvement in DAS28 scores
In subjects from all three treatment arms who were EULAR (moderate or good) non-responders at week 12, but became responders at week 24, their mean DAS28 scores showed a significant decrease from baseline to week 24 and from week 12 to week 24 ($p < 0.05$) (fig 2). In the non-responder to non-responder group, mean DAS28 scores at week 12 were similar to those in the non-responder to responder group, arguing against a “partial response” as the explanation for the later improvement for those patients. Of note, mean DAS28 scores in the 12-week non-responders/24-week responders improved significantly at 24 weeks, but not to the same extent as for subjects who achieved a response at 12 weeks.

Radiographic outcome at week 52
To determine if there was a slowing of radiographic progression in subjects who were ACR20 non-responders at week 12, but became responders at week 24 compared with week 12

Table 1 Radiographic outcome at week 52 in week 12 and week 24 responders

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>NP (%)</th>
<th>p Value</th>
<th>Mean TSS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETN + MTX week 12 responder</td>
<td>171</td>
<td>69.0</td>
<td>0.440</td>
<td>-0.53 (−0.880 to −0.185)</td>
</tr>
<tr>
<td>ETN + MTX week 24 responder</td>
<td>20</td>
<td>80.0</td>
<td>0.357</td>
<td>-1.35 (−2.472 to −0.234)</td>
</tr>
<tr>
<td>ETN week 12 responder</td>
<td>145</td>
<td>59.3</td>
<td>0.177</td>
<td>-0.23 (−0.690 to 0.216)</td>
</tr>
<tr>
<td>ETN week 24 responder</td>
<td>24</td>
<td>75.0</td>
<td>0.195</td>
<td>-0.19 (−1.043 to 0.662)</td>
</tr>
<tr>
<td>MTX week 12 responder</td>
<td>133</td>
<td>48.1</td>
<td>0.037</td>
<td>0.64 (0.078 to 1.202)</td>
</tr>
<tr>
<td>MTX week 24 responder</td>
<td>36</td>
<td>27.8</td>
<td>2.82</td>
<td>2.82 (−0.487 to 6.145)</td>
</tr>
</tbody>
</table>

ETN, etanercept; MTX, methotrexate; NP, non-progressor defined by TSS < 0; TSS, total Sharp score.
responders, the mean change in TSS and the percentage of non-progressors were evaluated at week 52. Results are shown in table 1. No statistically significant difference was observed in the mean TSS or the percentage of non-progressors between the 12-week versus the 24-week responders in the etanercept or etanercept plus methotrexate arms. In the methotrexate arm, however, the 24-week responders showed a significant increase in TSS at 52 weeks compared with the 12-week responders.

**Predictors of improvement in response**

No baseline characteristics or week 12 clinical variables (C-reactive protein, erythrocyte sedimentation rate, swollen joint count, tender joint count, Health Assessment Questionnaire, visual analogue scale for pain, physician global assessment and DAS28) were significantly associated with a delayed response at 24 weeks.

**DISCUSSION**

In this retrospective analysis, a substantial improvement in clinical response was observed between 12 and 24 weeks in subjects with rheumatoid arthritis in all three treatment arms from the TEMPO trial, including those who were non or partial responders at 12 weeks. The improvement in response at 24 weeks was most apparent in the etanercept plus methotrexate arm, in which 57.5% of ACR20, 46.8% of ACR50 and 51.1% of ACR70 non-responders became ACR20, ACR50 and ACR70 responders, respectively, at week 24. Similar improvements were observed for DAS28 scores in all three treatment arms.

The delayed response observed at 24 weeks was largely sustained in 80% of subjects to 52 weeks and was not associated with an inferior outcome with regard to the inhibition of radiographic progression at 52 weeks in the etanercept and etanercept plus methotrexate arms.

There are no clear guidelines on the appropriate treatment trial duration for TNF inhibitors. Recommendations from international guidelines vary, with most indicating 12 weeks as a time to assess response after TNF inhibitor therapy. Whereas some recommend discontinuing therapy at 12 weeks for non-responders, others allow for doctor’s discretion on whether or not to continue therapy.

Importantly, an analysis of disease variables and patient characteristics failed to identify any predictive factors.

Limitations of the current study include the retrospective nature of the analysis. Moreover, these findings are from patients enrolled in a randomised clinical trial who met the specific inclusion criteria and had high disease activity. Therefore, these observations may not reflect patients in a real-world setting.

In conclusion, findings from this retrospective analysis suggest that a significant proportion of patients who do not achieve a clinical response 12 weeks after the initiation of etanercept with or without methotrexate therapy may benefit from continuing therapy for up to 24 weeks. Additional benefits of continuing therapy for up to 24 weeks include the sustainability of the 24-week gain in response through at least one year while maintaining radiographic protection.

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**Ethics approval:** Ethics approval was obtained.
Contributors: Individual analyses for this study were designed by Amgen and Wyeth Pharmaceuticals. This specific report was designed by Amgen and Wyeth Pharmaceuticals with input from AK, LK and DvdH. Data analyses were run by JL. The authors developed the manuscript with writing assistance from Amgen Inc and made decisions about submission for publication in collaboration with Amgen.

REFERENCES
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