Review: Etanercept (25 mg subcutaneously twice weekly) reduces symptoms and disease activity in rheumatoid arthritis


**Question**
Is etanercept (ENC) effective for reducing symptoms and disease activity in patients with rheumatoid arthritis (RA)?

**Data Sources**
Studies were identified by searching electronic databases from 1966 to February 2003, hand-searching proceedings of major rheumatology conferences and bibliographies of relevant articles, and contacting content experts and pharmaceutical companies that manufacture ENC for unpublished studies.

**Study Selection and Assessment**
Studies were selected if they were randomized controlled trials (RCTs) or controlled clinical trials that lasted ≥ 6 months and evaluated the effectiveness of ENC in patients ≥ 16 years of age with active RA. Study quality was assessed using the Jadad scale.

**Outcomes**
Improvement in the American College of Rheumatology (ACR) core set of disease activity measures specified as ACR-20, ACR-50, and ACR-70 corresponding to 20%, 50%, and 70%, respectively, improvement in tender and swollen joint counts plus another corresponding 20%, 50%, or 70% improvement in 3 of the 5 remaining core measures of disease activity; NRCTs = number of randomized controlled trials. Other abbreviations defined in Glossary; weighted event rates, RBI, NNT, and CI calculated from data in article using a fixed-effects model.

**Main Results**
3 RCTs (955 patients) met the selection criteria. Effectiveness at 6-month follow-up: Comparisons were ENC (25 mg subcutaneously twice weekly) plus methotrexate (MTX) vs ENC placebo plus MTX (1 RCT) or ENC (25 mg and 10 mg subcutaneously twice weekly) vs placebo (1 RCT). Meta-analysis of the RCTs showed that rates of ACR-20 and ACR-50 responses were greater in the ENC group (at both 25- and 10-mg doses) than in the control group (MTX alone or placebo) (Table). The rate of ACR-70 response was greater in the ENC-25-mg group than in the control group (relative risk [RR] 11.35, 95% CI 2.19 to 58.30). Effectiveness at 12-month follow-up: 1 RCT compared ENC (25- and 10-mg doses) with MTX. The rate of ACR-50 response was lower in the ENC-10-mg group than in the MTX group (RR 0.75, CI 0.58 to 0.98). The ENC-25-mg and MTX groups did not differ for any of the ACR responses. Meta-analysis of all RCTs showed that fewer patients in the ENC-25-mg group than in the control group withdrew from the study (RR 0.43, CI 0.24 to 0.77).

**Conclusion**
Etanercept (25 mg subcutaneously twice weekly) reduces symptoms and disease activity in patients with rheumatoid arthritis.

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### Etanercept (25 mg or 10 mg subcutaneously twice weekly) vs control (methotrexate alone or placebo) in rheumatoid arthritis at 6 months*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>NRCTs (n)</th>
<th>Comparisons</th>
<th>Weighted event rates</th>
<th>RBI (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR-20 response</td>
<td>2 (247)</td>
<td>Etanercept, 25 mg vs control</td>
<td>63% vs 16%</td>
<td>284% (147 to 498)</td>
<td>3 (2 to 3)</td>
</tr>
<tr>
<td></td>
<td>1 (156)</td>
<td>Etanercept, 10 mg vs placebo</td>
<td>51% vs 11%</td>
<td>356% (137 to 777)</td>
<td>3 (2 to 4)</td>
</tr>
<tr>
<td>ACR-50 response</td>
<td>2 (247)</td>
<td>Etanercept, 25 mg vs control</td>
<td>40% vs 5%</td>
<td>789% (261 to 2089)</td>
<td>3 (3 to 4)</td>
</tr>
<tr>
<td></td>
<td>1 (156)</td>
<td>Etanercept, 10 mg vs placebo</td>
<td>24% vs 5%</td>
<td>374% (68 to 1236)</td>
<td>6 (4 to 13)</td>
</tr>
</tbody>
</table>

*ACR-20 and ACR-50 = American College of Rheumatology 20 and 50, respectively (corresponding, respectively, to 20% and 50% improvement in tender and swollen joint counts plus 20% and 50% improvement in 3 of the 5 remaining core measures of disease activity); NRCTs = number of randomized controlled trials. Other abbreviations defined in Glossary; weighted event rates, RBI, NNT, and CI calculated from data in article using a fixed-effects model.

**Commentary**
The methodological rigor of the review by Blumenauer and colleagues is commendable. Because 955 patients from diverse communities were included and because homogeneity was ensured by fulfilling ACR criteria for the diagnosis of RA and for responses to treatment in all RCTs selected, the results are valid, even if no 2 trials shared an identical design.

All RCTs showed that a 25-mg, twice-weekly, subcutaneous injection of ENC is well tolerated and effective in RA. However, not all RCTs were uniform. 2 examined persistently active RA despite previous therapy with MTX or similar drugs. Furthermore, 1 large RCT (n = 632), which enrolled patients with active early RA and no previous disease-modifying drug treatment, was much longer and the only one to assess radiographic bone erosions and joint space narrowing in a blinded manner (1). For patients whose disease remains florid despite high doses of MTX, switching to ENC or adding ENC constitutes a highly effective option. Because it is crucial to diagnose active RA and start “disease-modifying” treatment as early as possible to prevent irreversible joint damage (2), MTX, ENC, or both are good options initially. MTX is easier to administer and much less costly to the patient. It achieves rates of improvement that do not differ substantially from those achieved by ENC at 12 months, has a beneficial effect on erosions, and shows a similar rate of withdrawals, thus supporting its enduring value as monotherapy in active early RA.

However, the more rapid response, the considerably better radiographic outcomes, and the sustained improvement after 3 years in comparison with MTX (3) make ENC (25 mg twice weekly) an important initial treatment alternative in RA, either alone or combined with MTX. Nevertheless, additional longer-term studies are needed to evaluate the safety, cost-effectiveness, and continued efficacy of ENC.

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**References**