Etanercept plus methotrexate reduced symptoms and disease activity in adult-onset rheumatoid arthritis

Klareskog L, van der Heijde D, de Jager JP, et al. **Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial.** Lancet. 2004;363:675-81.

QUESTION

In patients with active adult-onset rheumatoid arthritis (RA), is a combination of etanercept (ENC) plus methotrexate (MTX) more effective than monotherapy with either agent for reducing symptoms and disease activity?

METHODS

Design: Randomized controlled trial (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes [TEMPO]).

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, and outcome assessors).*

Follow-up period: 52 weeks.

Setting: Australia, Europe, and Israel.

Patients: 682 patients > 18 years of age (mean age 53 y, 77% women) who had diagnosed, active adult-onset RA (defined as ≥ 10 swollen and ≥ 12 painful joints, and ≥ 1 of the following: erythrocyte sedimentation rate ≥ 28 mm/h, plasma C-reactive protein ≥ 20 mg/L, or morning stiffness for ≥ 45 min) for 6 months to 20 years (mean disease duration 6.6 y). Exclusion criteria included previous use of ENC or other tumor-necrosis factor (TNF) antagonists or immunosuppressive drugs ≤ 6 months before screening and any investigational drug or biological ≤ 3 months before screening.

Intervention: Patients were allocated to ENC (25 mg subcutaneously twice weekly) (n = 223), MTX (7.5 mg increased to 20-mg oral capsules once per wk within 8 wk if patients had any painful or swollen joints) (n = 228), or ENC plus MTX (combination group, n = 231).

Outcomes: Overall cumulative response (improvement) at 24 weeks measured by a numeric index of the American College of Rheumatology response area under the curve and change from baseline in total joint damage (modified Sharp score) at 52 weeks.

Patient follow-up: {88% at 24 weeks}†. Analysis was by intention to treat with last outcome carried forward for missing data. Data were available for < 80% of patients at 52 weeks.

MAIN RESULTS

At 24 weeks, cumulative improvement (reduction) in symptoms and disease activity was greater in the combination group than in either of the monotherapy groups (Table). Furthermore, cumulative improvement (reduction) in symptoms and disease activity was also greater in the ENC group than in the MTX group (Table).

CONCLUSION

In patients with active adult-onset rheumatoid arthritis, a combination of etanercept (ENC) plus methotrexate (MTX) was more effective than monotherapy with either agent for reducing symptoms and disease activity.

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*See Glossary.

†Information provided by author.

A combination of etanercept (ENC) plus methotrexate (MTX) vs monotherapy with either agent in active adult-onset rheumatoid arthritis‡

Outcome at 24 wk	Comparisons	Means	Difference (95% CI)
Numeric index of the American College of Rheumatology response area under the curve (percent-y)	Combination vs MTX	18.3 vs 12.2	6.1 (4.5 to 7.8) (P < 0.001)
	Combination vs ENC	18.3 vs 14.7	
	ENC vs MTX	14.7 vs 12.2	2.5 (0.8 to 4.2)

‡CI defined in Glossary.

COMMENTARY

Do TNF inhibitors offer a substantial advantage over MTX in the treatment of RA? And, should they be used in combination with MTX? The TEMPO study by Klareskog and colleagues is one of several studies attempting to answer these questions. It is similar in design to studies of other TNF inhibitors (adalimumab and infliximab) (1, 2) in that it enrolled patients with moderately severe RA and measured their self-assessment of disease, inflammatory mediators, radiographic erosion, and joint space narrowing. However, the TEMPO study differs from the others in several ways. First, patients had had RA for a mean duration of 6.6 years, which is neither early nor late disease. Second, only 43% of patients had used MTX previously. Patients naïve to MTX and those with early RA may be more responsive to treatment, and results from this study may therefore be somewhat more positive than those from other studies. Nonetheless, its conclusions are similar to those reached in other trials (1, 2, 3): TNF inhibitors combined with MTX are more effective than TNF inhibitors or MTX alone.

Does this mean that a clinician should start any patient with RA on combination therapy? If a patient is newly diagnosed with moderately severe RA, the studies suggest that the response to MTX alone is sufficient to merit an initial trial. If the same patient does not respond to MTX but can tolerate it, research and logic support a regimen that adds a TNF inhibitor to MTX rather than substituting for it.

2 questions about the long-term use of TNF inhibitors alone or in combination with MTX remain unanswered: Are they cost-effective, and being immunomodulators, will their use increase risk for lymphoma? Until these questions are answered, the message to primary practitioners is simple: Detect RA early and quickly refer the patient to a rheumatologist for consideration of either MTX or TNF inhibitors. If the patient does not respond to MTX alone, TNF inhibitors should be added.

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References

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