

# Etanercept was effective and safe for ankylosing spondylitis

Gorman JD, Sack KE, Davis JC, Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor  $\alpha$ . *N Engl J Med*. 2002;346:1349-56.

## QUESTION

In patients with active ankylosing spondylitis despite usual treatment, is treatment with etanercept more effective and safe than placebo?

## DESIGN

Randomized {allocation concealed\*}†, blinded {clinicians, patients, data collectors, outcome assessors, and monitoring committee}†, \* placebo-controlled trial with 4-month follow-up.

## SETTING

Rheumatology practices in northern California, United States.

## PATIENTS

40 patients  $\geq 18$  years of age (mean age 39 y, 78% men) who met the New York clinical criteria for definite ankylosing spondylitis and had evidence of active inflammatory spondylitis despite treatment. Exclusion criteria included spondylitis other than ankylosing spondylitis and clinical or radiologic evidence of complete spinal ankylosis. Follow-up was 93%.

## INTERVENTION

Patients were allocated to twice-weekly subcutaneous injections of etanercept, 25 mg ( $n = 20$ ), or placebo ( $n = 20$ ), for 4 months. Patients continued to take drugs that had

been previously prescribed for ankylosing spondylitis if doses had not been changed for  $\geq 4$  weeks before the study.

## MAIN OUTCOME MEASURES

The main outcome was treatment response, as measured by the composite end point of  $\geq 20\%$  improvement in  $\geq 3$  of 5 measures of disease activity (morning stiffness, nocturnal spinal pain [100 mm visual analogue scale, 0 = no pain and 100 = most severe pain], functional limitation [10-point scale, 0 = none and 10 = severe limitations], patient global assessment of disease activity [5-point scale, 0 = none and 5 = very severe], and joint swelling).

## MAIN RESULTS

Analysis was by intention to treat. More patients who received etanercept showed a treatment response than did those who received placebo (Table). Also, patients who received etanercept had a shorter duration of morning stiffness than did those who received placebo (25 vs 60 min,  $P < 0.001$ ); less nocturnal spinal pain (15 vs 38 mm,

$P < 0.001$ ); improved patient global assessment of disease activity (2 vs 3,  $P < 0.001$ ); and fewer functional limitations (2.2 to 3.1,  $P < 0.001$ ). No serious adverse effects were reported, and the groups did not differ for rates of adverse events.

## CONCLUSIONS

In patients with ankylosing spondylitis, 4 months of treatment with etanercept was effective and well tolerated. Treatment led to reduced duration of morning stiffness, reduced nocturnal spinal pain, improved patient global assessment of disease activity, and increased physical function.

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\*See Glossary.

†Information provided by author.

## Etanercept vs placebo for ankylosing spondylitis at 4 months†

Outcome	Etanercept	Placebo	RBI (95% CI)	NNT (CI)
Treatment response	75%	30%	150% (31 to 433)	2 (1 to 7)

†Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data provided by author.

## COMMENTARY

A life-long program of appropriate regular exercise is generally advised in the treatment of ankylosing spondylitis. Nonsteroidal anti-inflammatory drugs are used during the active phase of the disease (1). Also, group physical therapy and hydrotherapy, appropriate counseling, adaptations at home, and general lifestyle modifications are usually recommended (1). For persistent inflammatory disease not responding to these interventions, a disease-modifying antirheumatic drug may be introduced. In randomized trials, it has been shown that sulfasalazine modestly improved peripheral joint symptoms but not axial symptoms (1). Some inconclusive preliminary reports evaluating the role of methotrexate have also been published (1).

The study by Gorman and colleagues and a similar study by Braun and colleagues (2) provide hope for the treatment of these patients. However, this study has some methodological limitations. First, the number of patients is small and the duration of the treatment is short (only 4 mo) for a life-long disease. Second, up to 25% of patients used corticosteroids and up to 40% used disease-modifying antirheumatic drugs. Third, although the difference in proportions of patients reaching the study goal of 20% improvement between the treated and placebo groups is large, a 20% improvement in this composite score is not

clinically impressive. By comparison, studies in rheumatoid arthritis have shown improvements in the treated groups when 50% and even 70% improvement was used as a cut-off point (3).

Longer-term studies are needed to further explore the place of tumor-necrosis factor- $\alpha$  (TNF- $\alpha$ ) blockade in treating ankylosing spondylitis. It is still unclear whether TNF- $\alpha$  blockers can also be seen as disease-modifying drugs in ankylosing spondylitis, with clearly shown inhibition of radiographic progression.

Patients with ankylosing spondylitis frequently do well for many years with minimal treatment. Conversely, some patients suffer severely from their disease. If these patients could be identified early and if TNF- $\alpha$  blockade could slow disease progression, benefits in terms of patient comfort and quality of life would probably be substantial.

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## References

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2. Braun J, Brandt J, Listing J, et al. *Lancet*. 2002;359:1187-93.
3. Maini RN, Breedveld FC, Kalden JR, et al. *Arthritis Rheum*. 1998;41:1552-63.