



Read a commentary by Glenn D Rosen, MD, of Stanford University School of Medicine, on the clinical implications of the publication by Raghu G, et al (*Am J Respir Crit Care Med.* 2008;178:948-955.) entitled **"Treatment of Idiopathic Pulmonary Fibrosis with Etanercept: An Exploratory, Placebo-controlled Trial."**

## CLINICAL DESIGN

A phase 2 exploratory study examined the safety and efficacy of etanercept, an anti TNF- $\alpha$  agent, for the treatment of idiopathic pulmonary fibrosis (IPF). This double-blind, placebo-controlled trial randomized 46 patients to etanercept treatment and 41 to placebo. Patients were enrolled only if they had not shown improvement in pulmonary function in the prior 24 months, despite therapy with agents such as prednisone and azathioprine. The primary endpoints were change from baseline in FVC% predicted, DL<sub>CO</sub> % predicted, and change in P(A-a)O<sub>2</sub> gradient (at rest) at 48 weeks. Secondary endpoints included overall mortality, 6 minute walk distance (6MWD), St. George Respiratory Questionnaire (SGRQ), Mahler dyspnea score, radiographic progression, and others.

## ETANERCEPT TRIAL

<b>Mechanism</b>	TNF- $\alpha$ inhibitor
<b>Trial Design</b>	Randomized, placebo controlled, Phase 2
<b>Number of Patients</b>	87 (M = 59; F = 28)
<b>Treatment</b>	Etanercept 25 mg SC TIW vs placebo
<b>Inclusion Criteria</b>	FVC > 45% predicted (mean FVC 63.4%) DL <sub>CO</sub> > 25% predicted PaO <sub>2</sub> > 55 mm Hg/SpO <sub>2</sub> > 88%
<b>Primary Endpoints</b>	FVC % predicted DL <sub>CO</sub> % predicted A-a gradient
<b>Results</b>	Primary endpoint not met

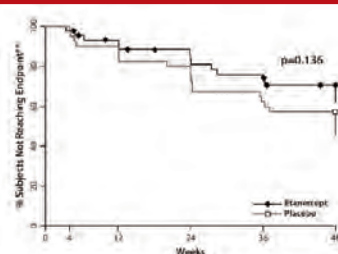
Raghu G, et al. *Chest.* 2005;128:496S-497S.

## RESULTS

Of the 87 patients who started the study, 65 patients (34 receiving etanercept and 31 receiving placebo) completed the study. There were no statistical differences in the three primary endpoints between treatment groups. However, the etanercept group did show less of a decline in FVC and DL<sub>CO</sub> and less of an increase in A-a gradient at 48 weeks. There were no statistical differences in secondary endpoints between treatment groups. For example, the 6MWD was improved in the etanercept group compared to

**FIGURE 1.**

**Kaplan-Meier plot of death/disease progression.**



No. at risk (no. of subjects remaining): etanercept: 45, 44, 39, 33, 29, and 22, for Weeks 0, 4, 12, 24, 36, and 48, respectively; placebo: 40, 39, 36, 30, 25, and 18, for Weeks 0, 4, 12, 24, 36, and 48, respectively.  
\*\*Death or disease progression (10% decline in FVC [L] or death).

the placebo group, but the difference was not significant. A post hoc analysis of the number of subjects experiencing death or disease progression (> 10% decrease in FVC) using a Kaplan-Meier plot (Figure 1) showed a slower progression in patients receiving etanercept, ( $P = 0.136$ ); and 55% of placebo patients versus 33.3% of etanercept patients met the endpoint ( $P = 0.052$ ).

There were 4 patients who died in the etanercept group and 2 in the placebo group ( $P = 0.41$ ), and none of the deaths were attributed to the drug. Adverse events were not statistically different

**TABLE 1.**

**Treatment-emergent adverse events reported at a frequency  $\geq 20\%$  in either group.**

Adverse Event	Etanercept (n = 46)	Placebo (n = 41)
Any noninfectious event	No. (%)	No. (%)
Total*	42 (91.3)	37 (90.2)
Cough increase	17 (37.0)	16 (39.0)
Dyspnea	12 (26.1)	11 (26.8)
Asthenia	8 (17.4)	11 (26.8)
Headache	7 (15.2)	11 (26.8)
Rhinitis	11 (23.9)	8 (19.5)
Any infectious event		
Total	29 (63.0)	28 (68.3)
Upper respiratory infection	15 (32.6)	13 (31.7)
Bronchitis	10 (21.7)	11 (26.8)

\*Excluding injection site reactions.

between treatment groups except for an increase in injection site redness in the etanercept group.

## DISCUSSION

This study was motivated by animal and human data suggesting that TNF- $\alpha$  plays a role in the pathogenesis and/or progression of IPF. In this study, Raghu et al did not reveal a benefit of etanercept treatment for patients with IPF. However, the study was underpowered to detect a statistically significant difference in efficacy between the treatments; only 65 patients (75%) completed the study. Although the authors suggest this high dropout rate was observed in the IFIGENIA and BUILD 1 trials, it is much higher than the < 10% dropout rates in the two IFN- $\gamma$  trials for IPF (GIPF-001 and INSPIRE). The reason for the high dropout rate is unclear. Patients in this study, unlike prior trials, had not responded to other treatments and were not permitted concurrent therapy such as low dose prednisone. It is intriguing that fewer patients on etanercept (33.3%) than placebo (55%) showed disease progression (> 10% decline in FVC from baseline) or death, though the difference was not significant ( $P = 0.052$ ). In fact, 4 patients died on etanercept versus 2 on placebo, suggesting that fewer patients in the etanercept group experienced an FVC decline of > 10%. It is possible, therefore, that etanercept reduces the risk of disease progression.

Acute exacerbations of IPF were not recorded in this study. However, the small sample size at baseline, diminished by a high dropout rate, limits the statistical power of this study to detect a difference between etanercept and placebo treatment. In summary, even though there was a trend suggesting slower disease progression for patients on etanercept versus placebo, no positive conclusions about its benefit or efficacy should be made based on this study.

Raghu G, Brown RK, Costabel V, et al. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. *Am J Respir Crit Care Med.* 2008;178:948-955.