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Journal club critique
Afelimomab led to a modest mortality benefit in patients with severe sepsis and elevated interleukin-6 levels

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Expanded Abstract

Citation

Panacek EA, Marshall JC, Albertson TE, Johnson DH, Johnson S, MacArthur RD, Miller M, Barchuk WT, Fischkoff S, Kaul M, Teoh L, Van Meter L, Daum L, Lemeshow S, Hicklin G, Doig C: Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab')2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. Crit Care Med 2004, 32:2173-2182 [1].

Hypothesis

Afelimomab, a fragment of murine monoclonal antibody to human TNF-α, reduces 28-day all-cause mortality in patients with severe sepsis and elevated serum IL-6 levels.

Methods

Design: Prospective, randomized, double-blind, placebo-controlled, multi-center, phase III clinical trial.

Setting: One hundred fifty-seven intensive care units in the United States and Canada.

Subjects: 2,634 patients with severe sepsis secondary to documented infection, of whom 998 had elevated IL-6 levels.

Intervention: Patients were stratified into two groups by means of a rapid qualitative interleukin-6 test kit designed to identify patients with serum interleukin-6 levels above (test positive) or below (test negative) approximately 1000 pg/mL. Of the 2,634 patients, 998 were stratified into the test-positive group, 1,636 into the test-negative group. They were then randomly assigned 1:1 to receive afelimomab 1 mg/kg or placebo for 3 days and were followed for 28 days. The *a priori* population for efficacy analysis was the group of patients with elevated baseline interleukin-6 levels as defined by a positive rapid interleukin-6 test result.

Outcomes: The primary outcome was 28-day all-cause mortality. Secondary outcomes included improvement in organ dysfunction, reduction in TNF and IL-6 levels, and safety.

Results

In the group of patients with elevated interleukin-6 levels, the mortality rate was 243 of 510 (47.6%) in the placebo group and 213 of 488 (43.6%) in the afelimomab group (p=0.21). Using a logistic regression analysis, treatment with afelimomab was associated with an adjusted reduction in the risk of death of 5.8% (p = .041) and a corresponding reduction of relative risk of death of 11.9%. Mortality rates for the placebo and afelimomab groups in the interleukin-6 test negative population were 234 of 819 (28.6%) and 208 of 817 (25.5%), respectively (p=0.16). In the overall population of interleukin-6 test positive and negative patients, the placebo and afelimomab mortality rates were 477 of 1,329 (35.9%)and 421 of 1,305 (32.2%), respectively (p=0.049). Afelimomab resulted in a significant reduction in tumor necrosis factor and interleukin-6 levels and a more rapid improvement in organ failure scores compared with placebo. The safety profile of afelimomab was similar to that of placebo.

Conclusion

Afelimomab is safe, biologically active, and well tolerated in patients with severe sepsis, reduces 28-day all-cause mortality, and attenuates the severity of organ dysfunction in patients with elevated interleukin-6 levels.

Commentary

Sepsis and multiple organ dysfunction syndrome are leading causes of morbidity and mortality in the ICU [2]. Modulating the endogenous host inflammatory response toward the goal of improving survival for septic patients has been the holy grail of critical care researchers for some

time. Nearly sixty randomized controlled clinical trials have been conducted in this area, yet no new agents have been introduced into clinical practice [3]. In multiple studies of anti-TNF-α therapies, there have been no statistically significant improvements in survival in the experimental cohorts; indeed, in at least one study, survival was actually worsened in the group receiving the new agent. A meta-analysis of these trials suggested a small, but significant benefit for anti-TNF-α agents [3].

It is upon this background that we consider the study by Panacek and colleagues [1]. Their study is unique in that it is the first cytokine-based antisepsis trial to target specific subgroups of septic patients on the basis of a biochemical marker (serum IL-6 concentration). Increased IL-6 levels correlate with severity of illness and are associated with a poor outcome in septic patients. TNF-α is a proximal stimulus for IL-6 release. Hence, patients with elevated IL-6 levels could potentially benefit from an anti-TNF-α approach.

In this study, 2634 patients with severe sepsis were randomized to a 3-day course of afelimomab, a fragment of a murine monoclonal antibody to human TNF-α, or placebo. Prior to randomization, patients were classified as having either high (>1000 pg/ml) or normal serum IL-6 concentration via a rapid qualitative bedside assay. The primary *a priori* population for efficacy analysis was the subgroup of patients with elevated IL-6 levels (n=998). The authors found that mortality was lower in the high IL-6 patients that received afelimomab (43.6% versus 47.6%, p=0.21), though this difference only achieved statistical significance after adjusting for subtle baseline differences between groups. There were no differences in adverse events between groups, but human anti-mouse antibodies formed in nearly one quarter (23.6%) of afelimomab-treated patients. The authors concluded that afelimomab was safe and reduced mortality in septic patients with elevated IL-6 levels.

This study has a number of strengths. It is the largest prospective, multi-center, double-blind, randomized controlled trial in severe sepsis completed to date. Follow-up was complete in all patients and co-interventions, such as adequate antibiotic therapy, surgical interventions, and other supportive care, were similar between groups. By focusing on patients with elevated IL-6 levels, the authors selected a group at high risk of mortality, and by extension, the group with arguably the most to gain from treatment.

A few limitations of this study deserve consideration. First, randomization failed to balance some clinically relevant factors among groups. For instance, sequential organ failure assessment (SOFA) scores trended higher in subjects that received active drug (11.2 vs. 10.8, p=0.058). Differences in baseline characteristics likely explain why the improvement in mortality seen with afelimomab was only significant after multivariable modeling, though it would have been helpful for the authors to have provided more details about these models. Second, the mortality benefit of afelimomab was small relative to that seen with another recent addition to the sepsis armamentarium, drotrecogin alfa (activated) [4] (relative risk reduction, 11.9% vs.19.8%) [5]. Conceivably, a combination of these two agents might yield even greater

reductions in mortality. Third, while no clinical sequelae were associated with the development of human anti-mouse antibodies, the frequent occurrence of these antibodies raises concern about the future use of other antibody-based therapies, such as abciximab, in these patients. Fourth, there are questions about the practicality of rapid IL-6 testing at the bedside in routine clinical practice. Finally, the results of this trial, which completed enrollment June 1999, were not published until November 2004. Delayed manuscript rejections and a change in the company owning the product and their internal review process were some of the circumstances that led to this unfortunate delay (Ed Panacek, personal communication).

Recommendation

Afelimomab appears to be safe and may improve mortality in the subset of septic patients with high IL-6. However, outside the setting of randomized clinical trials, we cannot recommend its routine use. Further study is needed to determine if addition of afelimomab to already existing proven therapies, such as drotrecogin alfa (activated) or steroids [6], leads to additional mortality benefits in severe sepsis.

Competing interests

The authors declare that they have no competing interests.

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