Drug does not significantly reduce risk of death among patients with severe sepsis

March 19 2013

Administration of the drug eritoran to patients with severe sepsis and septic shock failed to demonstrate a significant effect on reducing all-cause 28-day mortality or 1-year mortality, compared with placebo, according to a study in the March 20 issue of *JAMA*.

Severe sepsis, a syndrome of acute infection complicated by organ dysfunction, is caused by a dysregulated systemic inflammatory response. Sepsis can progress to systemic hypotension (septic shock), multiple organ dysfunction, and death. "Lipopolysaccharide (LPS) or endotoxin, the major component of the outer membrane of gram-negative bacteria, is a potent stimulator of the inflammatory response. LPS triggers inflammation in gram-negative sepsis," according to background information in the article. Eritoran, a synthetic analog (a substance that is similar, but not identical, to another) of lipid A, is a potent and specific antagonist of LPS action. In a phase 2 trial, eritoran-treated patients at high risk of death had lower mortality that was not statistically significant.

Steven M. Opal, M.D., of the Alpert Medical School of Brown University, Providence, R.I., and colleagues conducted a phase 3 trial to evaluate the safety and efficacy of eritoran in reducing mortality in patients with severe sepsis. The randomized, multinational trial was conducted in 197 intensive care units. Patients were enrolled from June 2006 to September 2010 and final follow-up was completed in September 2011. Patients with severe sepsis (n=1,961) were randomized and treated within 12 hours of onset of first organ dysfunction in a 2:1

ratio with a 6-day course of either eritoran tetrasodium (105 mg total) or placebo, with n=1,304 and n=657 patients, respectively. The primary end point for the study was 28-day all-cause mortality. The secondary end points were all-cause mortality at 3, 6, and 12 months after beginning treatment.

The researchers found that treatment with eritoran did not result in significant reductions in the primary study end point of 28-day mortality in the modified intent-to-treat analysis (randomized patients who received at least 1 dose) population; 28.1 percent (366/1,304) of patients in the eritoran group vs. 26.9 percent (177/657) of patients in the placebo group.

There was also no significant difference in the secondary end point of 1-year all-cause mortality: 44.1 percent (290/657) in the eritoran group vs. 43.3 percent (565/1,304) in the placebo group.

Eritoran was well tolerated with comparable numbers of treatment-emergent adverse events (TEAEs) and serious TEAEs between eritoran and placebo groups.

"These findings are in contrast with several preclinical studies and in phase 1 clinical trials in which eritoran terminated lipopolysaccharide-associated molecular and clinical events when administered in adequate doses. Despite these promising early results, no evidence of significant benefit was observed with eritoran in this large phase 3 trial," the authors write. "Eritoran joins a long list of other experimental sepsis treatments that do not improve outcomes in clinical trials in these critically ill patients."

More information: *JAMA*. 2013;309(11):1154-1162