Risk of Sepsis Death Soars With Antibiotic Delays

BY JANE SALODOF MACNEIL Contributing Writer

PHOENIX, AZ. — Risk of death from sepsis increases by 6%-10% with every hour that passes from the onset of septic shock until the start of effective antimicrobial therapy, according to a re-analysis of Recombinant Human Activated Protein C; it mimics endogenous protein C, it inhibits coagulation and inflammation when activated. Waiting 2 or more days to initiate the drug predicted hospital mortality, whereas earlier initiation predicted lower hospital costs and shorter lengths of stay among survivors, reported Mr. Ernst, a pharmacist at Eli Lilly & Co., Indianapolis.

In a study funded by Lilly, Mr. Ernst and his associates studied an online database records of 1,179 patients who received drotrecogin alfa during their hospital stay following evident severe sepsis, defined as hemorrhage anted at ventricular use plus vasodilator and/or vasopressor use. The records were obtained from a large national database of hospital discharge records maintained by Solucient, a health information technology company.

Of the 1,179 patients, 509 received drotrecogin alfa on the same day that they had evident severe sepsis (same-day patients), 354 received the drug the day after they had evident severe sepsis (next-day patients), and 325 received the drug 2 days or more after they had evident severe sepsis (day 2-plus patients). At ICU admission, day 2-plus patients had fewer organ dysfunctions than did patients in the other two groups. But between ICU admission and initiation of drotrecogin alfa, organ dysfunctions increased significantly more among day 2-plus patients than did next-day and same-day patients.

Hospital mortality was predicted by ventilator use (odds ratio [OR] 5.3), vasopressor use (OR 2.6), and initiation of drotrecogin alfa on day 2-plus (OR 1.7). Among survivors, 7% shorter length of stay and 10% lower adjusted post-drotrecogin alfa administration costs were predicted by same-day or next-day initiation.

Limitations of the study were its retrospective design and the fact that the database used contained limited clinical information, Mr. Ernst noted.

Xigris May Not Be Appropriate For Less Critically Ill Patients

BY MICHELE G. SULLIVAN Mid-Atlantic Bureau

Drotrecogin alfa (Xigris) is indicated only for adult patients with severe sepsis who are at high risk of death, may not be appropriate for patients with single organ dysfunction and recent surgery, and should only be administered after careful consideration of the potential risks and benefits, according to a new warning by Eli Lilly & Co., which manufactures the drug. Lilly added the warning to the prescribing information after two studies indicated a small but clinically important increase in the rate of all-cause mortality among these patients treated with the agent, compared with those who received placebo. Physicians and other health care providers received a letter in February alerting them to the new warning.

Drotrecogin alfa (Xigris) is indicated only for adult patients with severe sepsis who are at high risk of death. The subset of patients with single organ dysfunction and recent surgery, “may not be at high risk of death, and therefore may not be in need of Xigris,” the warning states.

The warning was based on a preliminary analysis of the Administration of Drotrecogin Alfa [Activated] Early Stage Severe Sepsis (ADDRESS) randomized, placebo-controlled trial and a re-analysis of Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS), the drug’s phase III registration trial. In the PROWESS trial of almost 1,700 patients, only 98 had single organ dysfunction and recent surgery (within 30 days of therapy). Among the 49 treated patients, 10 died within 28 days of treatment and 14 were hospitalized; among the placebo-treated patients, 8 died within 28 days and 8 were hospitalized.

The ADDRESS trial studied the drug’s effect in patients who were less critically ill (Acute Physiologic and Chronic Health Evaluation [APACHE] II score less than 25, or single sepsis-induced organ failure at any APACHE II score). Among 123 treated patients, 67 died within 28 days and 76 were hospitalized; among the placebo-treated patients, 44 died within 28 days and 62 were hospitalized.

“The important thing to note is that this is a preliminary finding,” said Carole Pul, spokesperson for Lilly. “We issued the warning because we felt these patients may not be at high risk for death and so the drug is not indicated for them.”

During Food and Drug Administration approval hearings for drotrecogin alfa, members of the Anti-Infective Drugs Advisory Committee noted that the drug was less effective in reducing mortality in patients with less severe sepsis, who had a better prognosis. The main safety concern during the hearings was serious bleeding events, which the company said appeared to be associated with vesel trauma or severe coagulopathy and were consistent with the product’s antithrombotic and prothrombin effects. Serious bleeding adverse events occurred in 3.5% of those on drotrecogin alfa, compared with 2% of those on placebo. Of the serious bleeding events among those on drotrecogin alfa, most occurred during or immediately after the patient received the drug. Most bleeding sites were gastrointestinal, intrabdominal, intrathoracic, retroperitoneal, intracranial, genitourinary, and skin/soft tissue.

The investigation started with animal studies. In those experiments, mortality was held to 10% if the animals were given an antibiotic within a 12-hour window before the onset of hypotension, according to Dr. Kumar. The mortality became 80% if the antibiotic was started 15 hours afterward, and 100% at 24 hours.

In the human retrospective study reported at the meeting, 89% of patients who received an appropriate antibiotic within the first half hour survived, he said. By the second hour, the survival rate dropped to 84%, and it continued to drop at a rate of 7.5% every hour thereafter.

Subset analyses by antibiotic order showed that drotrecogin alfa, compared with 2% of those on placebo. Of the serious bleeding events among those on drotrecogin alfa, most occurred during or immediately after the patient received the drug. Most bleeding sites were gastrointestinal, intrabdominal, intrathoracic, retroperitoneal, intracranial, genitourinary, and skin/soft tissue.

’t ...that’s a translation to a 15% absolute improvement in mortality.’

Time to effective antibiotics. If the first choice is not effective, the effects of any initial delay can be all the more overwhelming, he said.

Dr. Kumar called for hospitals to use medical response teams with algorithm protocols for patients in septic shock. He reported that his hospital has instilled the following changes in response to the study:

► Staff can start intravenous antibiotics in hypotensive sepsis patients without waiting for approval.

► Nurses have been told that the first dose of any new antibiotic is an automatic stat order.

► No sepsis patient is transferred to an intensive care unit without receiving an antibiotic before leaving the emergency department.

Many physicians do not realize that an antibiotic order in the emergency department time to treat was 4.5-5 hours, he said. By the second hour, the survival rate dropped to 84%, and it continued to drop at a rate of 7.5% every hour thereafter.

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For Less Critically Ill Patients

BY DOUG BRUNK San Diego Bureau

SEATTLE — When it comes to initiating therapy with drotrecogin alfa in patients with severe sepsis, the earlier the better.

That’s the key message from a large study of patients who received drotrecogin alfa (Xigris) at 139 hospitals in the United States between November 2001 and June 2003, Frank Ernst, Pharm. D., reported at the annual meeting of the American College of Chest Physicians.

Drotrecogin alfa (activated) is recombinant human activated protein C; it mimics endogenous protein C, it inhibits coagulation and inflammation when activated. Waiting 2 or more days to initiate the drug predicted hospital mortality, whereas earlier initiation predicted lower hospital costs and shorted lengths of stay among survivors, reported Mr. Ernst, a pharmacist at Eli Lilly & Co., Indianapolis.

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