Warning Added to Xigris Prescribing Information

Xigris is indicated only for adult patients with severe sepsis who are at high risk of death.

BY MICHELE G. SULLIVAN
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Drotrecogin alfa, a biologic agent used to treat adults 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 be administered only 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 indicated for 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 reanalysis 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 patients treated with placebo, eight died within 28 days and eight were hospitalized.

The ADDRESS trial studied the drug's effect in patients who were less critically ill (Acute Physiology and Chronic Health Evaluation [APACHE] II score less than 25, or single sepsis-induced organ failure at any APACHE II score). Among 323 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 Puls, 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 vessel trauma or severe coagulopathy and were consistent with the product's antithrombotic and profibrinolytic 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 patients received the infusion. Bleeding sites were gastrointestinal, intraabdominal, intrathoracic, retroperitoneal, intracranial, genitourinary, and skin/soft tissue.

Drotrecogin alfa is a genetically engineered version of human activated protein C. This molecule is a naturally occurring protein that, when activated, promotes fibrinolysis, inhibits thrombosis and inflammation, and is an important modulator of the coagulation and inflammation associated with severe sepsis, according to Lilly. Evidence suggests that the process that activates the molecule may be impaired by sepsis, and therefore, septic patients have low levels of activated protein C. ■

Six-Hour, Rapid-Intervention Protocol For Sepsis Cuts Mortality Rate in Half

BY JANE SALODOF MACNEIL
Contributing Writer

PHOENIX, ARIZ. — The emergency department at a California hospital has reduced in-hospital sepsis mortality from 42% to 22% with a 6-hour protocol of rapid interventions, H. Bryant Nguyen, M.D., reported at a meeting sponsored by the Society of Critical Care Medicine.

Data on 208 sepsis patients treated from the start of the program in October 2003 through the end of 2004 show that the greatest benefit occurs when the protocol is completed on time, said Dr. Nguyen of Loma Linda (Calif.) University.

Mortality was 12.5% among the 24 patients who received all of the interventions within 6 hours, but was 34.2% among the 184 patients in whom the "STOP Sepsis Bundle" protocol was started but not completed within 6 hours. The difference in mortality was highly significant ($P = .008$).

STOP stands for Strategies to Timely Obviate the Progression of sepsis in the emergency department. Dr. Nguyen modeled the STOP Sepsis Bundle protocol after the 6-hour Severe Sepsis bundle promoted by the Institute for Healthcare Improvement (IHI) and the international Surviving Sepsis Campaign (SSC). Despite strong support for such an intervention, no one had previously established that it was viable in a working emergency department. "Most of this is not currently performed in most emergency departments around the country, so the feasibility of implementing the 6-hour bundle is unknown," he said.

As presented by Dr. Nguyen, Loma Linda's STOP Sepsis Bundle is set in motion for patients who meet three criteria: systemic inflammatory response syndrome (SIRS), a source of infection, and any one of the following: a systolic blood pressure less than 90 mm Hg after a 20 mL/kg fluid bolus, a serum lactate level of 4 mmol/L or higher, or more than one acute organ dysfunction.

The protocol comprises five components, of which the first three must be completed within 6 hours:

- Begin hemodynamic monitoring (central venous pressure [CVP] and central venous oxygen saturation [$ScvO_2$]) within 2 hours.
- Start broad-spectrum antibiotics within 4 hours.
- Use early goal-directed therapy (EGDT), with these goals to be achieved within 6 hours and maintained until admission: CVP of at least 8 mm Hg, mean arterial pressure (MAP) of at least 65 mm Hg, and $ScvO_2$ of at least 70%.
- Obtain serial lactate levels to monitor for lactate clearance.
- Initiate corticosteroid treatment if the patient is on a vasopressor.

Dr. Nguyen said he focused on goals to be achieved rather than methods in customizing the SSC/IHI bundle. His modifications drew praise from Jean-Louis Vincent, M.D., a member of the SSC panel who worked on its sepsis bundle. Dr. Vincent, chair of the department of intensive care at Erasme University Hospital in Brussels, chaired the sepsis research session at the meeting.

"You have not really implemented the bundle of the Surviving Sepsis Campaign," he told Dr. Nguyen. "You have implemented a better bundle. … You changed it to improve it."

"There is only so much in 6 hours you can do, no matter how you word it," Dr. Nguyen said in his response.

He described a gradual implementation process in which bundle components were added at 3-month intervals. The phase-in started with staff education, and included nursing in-service training sessions every 6 months, grand rounds, quality improvement reports every 2 months, and continuous review of data.

"EGDT is easy to initiate but appears to be the most challenging component to complete," said Dr. Nguyen, a former student of EGDT champion Emanuel P. Rivers, M.D., at Henry Ford Hospital, Detroit.

Patients who received the complete bundle not only had a survival advantage, they also had shorter lengths of stay in the hospital (although the difference was not statistically significant): 8.1 days vs. 11.9 days for the larger cohort of sepsis patients ($P = .06$). "Completion of the bundle is associated with improved outcome and possibly a decrease in resource consumption in terms of length of stay," he concluded.

The staff has reached the point where it is comfortable with the arduous protocol, he added. "We treat them [sepsis patients] as a trauma patient. We treat them as a cardiac arrest patient. We invest the time for 2-3 hours," he said. "If we don't, in 6 hours they arrest." ■

Small Serum Creatinine Increases Predict Early Deaths in Severe Sepsis

PHOENIX, ARIZ. — Small increases in serum creatinine that are not currently viewed as signaling renal dysfunction are highly predictive of mortality in patients with severe sepsis, William Macias, M.D., reported at a meeting sponsored by the Society of Critical Care Medicine.

In a review of data on 1,226 patients, 28-day mortality reached 42.9% in patients whose creatinine rose by 0.2-0.49 mg/dL from baseline during the first 24 hours, said Dr. Macias of Lilly Research Laboratories in Indianapolis.

When an increase in creatinine met or exceeded the current marker of 0.5 mg/dL on day 1, 57.7% of patients died within 28 days. Mortality was 25.7% for patients with early increases of less than 0.2 mg/dL.

"The current definition may be too insensitive to detect acute kidney injury in patients with severe sepsis," Dr. Macias said. Relative serum creatinine increases that are greater than 25%—as well as acute increases of 0.5 mg/dL or greater—are associated with significant increases in mortality.

The researchers drew the patient population from placebo groups in the Integrated Database of Severe Sepsis and Xigris Therapy, a repository of data from trials for Lilly's drotrecogin alfa activated. The investigators were interested in patients with moderate increases of 0.2-0.49 mg/dL in serum creatinine because these are not currently associated with kidney injury.

"If you have increases from 0.2 to less than 0.5 [mg/dL], you have mortality of 40%" regardless of baseline level, Dr. Macias said. "If you have increases greater than 0.5 [mg/dL], you have mortality greater than 50%—no matter where they started."

Deaths typically occurred within 5 days if creatinine levels rose on day 1. Patients with high baseline creatinine that did not rise tended to die after day 15. "It was the same pattern over and over again. If you have an increase in creatinine you pay a very, very early penalty," he said.

—Jane Salodof Macneil