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
Mid-Atlantic Bureau

Drotrecogin alfa, a biologic agent used to treat severe sepsis, was an important intervention for patients who were at high risk of death, but it 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.

Liadi added to the warning the prescribing information after two studies indicated a small but clinically important increase in the rate of all-cause mortality among patients who met the criteria and were 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, said Dr. Nguyen, a former student of EGDT, who championed Emanuel P. Rivers, M.D., a member of the SSC panel and a former student of EGDT, who championed Emanuel P. Rivers, M.D., a member of the SSC panel and recent surgery.

“Tachyphylaxis is a reasonable explanation for this finding, but it is a preliminary finding,” said Carole Puls, spokesman 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.”

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

BY JANE SALOODOF MACNEIL
Contributing Writer

**Phoenix, Az. —** 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 showed 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 = 0.008).

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. Dr. Nguyen has 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 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 [ScVO2]) within 2 hours.
- Begin broad-spectrum antibiotics within 4 hours.
- Use early goal-directed therapy (EGDT), with these goals being achieved in 6 hours and maintained until admission: CVP of at least 8 mm Hg, mean arterial pressure (MAP) of at least 65 mm Hg, and ScVO2 of at least 70%.
- Obtain serial lactate levels to monitor for lactate clearance.
- Initiate corticosteroid treatment if the patient is on a vasoressor.

“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 = 0.06). Completion of the bundle is associated with improved outcome and possibly a decrease in resource consumption in terms of length of stay,” he concluded.

A departmental survey revealed that the staff typically occupied the point where it is comfortable with the arduous protocol, he added. “We treat them [sepsis patients] as a trauma patient,” Dr. Nguyen said. “We treat them as a cardiac arrest patient. We invest the time in 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.”

The staff typically occupied the point where it is comfortable with the arduous protocol, he added. “We treat them [sepsis patients] as a trauma patient,” Dr. Macias said. “We treat them as a cardiac arrest patient. We invest the time in 2-3 hours,” he said. “If we don’t, in 6 hours they arrest.”

—Jane Saloodof Macneil