Trial failure prompts soul-searching for critical-care specialists

In late May, researchers delivered the final analysis of the boldly named PROWESS-SHOCK trial. Despite the study's gallant moniker, though, the antisepsis drug Xigris (activated protein C) showed little prowess—and the results came as no shock, as Eli Lilly, the Indiana-based drugmaker behind the medicine, had already withdrawn Xigris from worldwide markets in October 2011. At the end of the day, global sales of Xigris came in at only $104 million in 2010, the last full year the agent was in use. But the PROWESS-SHOCK study continues to be a point of contention in the sepsis field as researchers dispute whether the results of randomized trials in the sepsis arena can fully be trusted.

"The outcome of [PROWESS-SHOCK] was not only bad for Lilly and activated protein C, but it was really bad for the entire field," says Steven Opal, an infectious disease specialist at the Brown University School of Medicine in Providence, Rhode Island.

For one thing, says Derek Angus, a critical-care physician at the University of Pittsburgh in Pennsylvania who sat on the data and safety monitoring board for the PROWESS-SHOCK trial, the whole Xigris story is "a bit of a faith shaker around how much of a house of sand are we building here" with clinical trials for sepsis. "The whole potential fickleness of this is quite disconcerting," he says.

Lilly's decision to pull Xigris came nearly a decade after US and European regulators approved the drug off the back of the first phase 3 PROWESS trial. That 1,700-person study was stopped early, in June 2000, because Xigris's results seemed so amazing: a reduction in 28-day mortality from 31% in the placebo group to 25% in Xigris-treated individuals (*N. Engl. J. Med.* **344**, 699–709, 2001). Yet subsequent findings proved disappointing. Additional trials requested by the US Food and Drug Administration (FDA), one in less ill adults and another in children with severe sepsis, did not show a benefit for Xigris (*N. Engl. J. Med.* **353**, 1332–1341, 2005; *Lancet* **369**, 836–843, 2007), and, like PROWESS, both studies were stopped prematurely—in these cases, however, for futility, rather than efficacy, reasons.

The PROWESS-SHOCK trial came about at the behest of the European Medicines Agency, which requested another large study of Xigris after numerous critics pointed out aspects of the original PROWESS design and implementation that may have helped yield a favorable result. For example, organizers changed the enrollment criteria halfway through the PROWESS trial to include more participants at high risk of death. Upon retesting, Xigris ultimately failed to reduce mortality in patients with septic shock in the PROWESS-SHOCK trial, a finding that has cast further doubt on the integrity of the first study.

Darron Cummings / Associated Press

Lilly-livered: The post-marketing PROWESS-SHOCK trial spurred Lilly to withdraw its antisepsis drug.

Which trial results do you believe?

Some researchers now think both trials were valid but came to different conclusions simply because of improvements in general sepsis management over the past decade that improved the survival rate of the control group and thereby diminished the comparative influence of the drug. Researchers involved in PROWESS-SHOCK had originally expected a 28-day survival rate in the placebo group below 70%, as was seen in PROWESS. But what they eventually saw was a rate of 76%. "When you have a moving target of placebo mortality and improvements in the standard of care, that adds additional challenges to running these types of studies, which are already very complicated and difficult," notes Jonathan Janes, medical director for acute care with Lilly.

Against that backdrop, PROWESS-SHOCK may have been underpowered to detect a significant benefit for Xigris. "This is a study that's negative for Xigris but positive for critical-care medicine," says Marco Ranieri, an anesthesiologist and intensive-care physician at the University of Turin in Italy. Or, perhaps, Xigris is now superfluous given the state of modern medicine, notes Taylor Thompson, director of the medical intensive care unit at the Massachusetts General Hospital in Boston who, together with Ranieri, led the PROWESS-SHOCK trial. "What we've got is a clinical trial of well-resuscitated, well-treated patients, and in that setting you don't need Xigris," he says.

But not everyone has such confidence in the latest study's results, given the logistical issues of running a placebo-controlled trial of an already approved medicine. Opal notes that many of the clinical centers that participated in the original PROWESS trial refused to take part in the follow-up, and he suspects that those sites that did enroll individuals in PROWESS-SHOCK—and were thus willing to give a placebo—might have been prejudiced, subconsciously or otherwise, against the drug from the get-go. "If you take the better places out of the globe and you exclude them from the study, it's possible that you've biased the study for failure rather than success," he says.

Guido Bertolini, a clinical epidemiologist who specializes in intensive care at the Mario Negri Institute for Pharmacological Research in Bergamo, Italy, also worries about the "dangerous precedent" that such a trial poses. "The idea to look for a confirmatory trial on efficacy without withdrawing the drug from the market is unbelievable from an ethical perspective," he says.

Not to worry, argues Thompson. "Reading the tea leaves from the FDA, my guess is that they'll never do this again," he says. "They'll ask for two trials" before granting approval for antisepsis drugs.

That may help mitigate some concerns. But, given the cost and uncertainty of such trials, the need for large-scale replication could have a chilling effect on the whole field. "It's going to take the financial incentive that was mildly present in the past to do these sepsis trials out of the equation," Opal says.

Elie Dolgin