Over the past thirty years or so, we have seen multiple therapies related to sepsis management that appeared beneficial in initial clinical trials but were later found to be useless or even harmful. Examples include goal-directed resuscitation to achieve maximal oxygen delivery, steroids for ARDS, tight glycemic control, and adrenal replacement therapy, among others. An overview of the history of evidence-based critical care medicine provides a strong argument for humility and caution. The story of Xigris provides another chapter for the fellows to consider as they move forward in their careers, and are asked to appraise new therapies that come along.

The story of activated protein C – also designated as drotrecogin alfa (recombinant) - or Xigris® began with stellar expectations. The PROWESS trial was published in the NEJM in 2001 (1). It was a randomized controlled trial that enrolled 1690 patients, comparing 28-day survival of patients treated with Xigris vs. placebo in the treatment of severe sepsis. The study was prematurely stopped at an interim analysis when it was observed that the mortality of the placebo group was significantly higher than that of the treatment group (30.8 vs. 24.7% - p=0.005). The risk of serious bleeding with Xigris (an antithrombotic agent) was found to be 3.5% versus 2% with placebo (p=0.06).

Tonya Whiting – our fellow that reviewed PROWESS – is in good company when she concluded that the results were believable. PROWESS seemed to be well-designed and had apparent strong internal validity. I remember feeling the same way back in 2001. I am always skeptical about new therapies, but I had to grudgingly admit that Xigris seemed to work – albeit in a select group of patients.

But the first time I gave Xigris to a patient, they suffered an intracranial hemorrhage.

I double-checked the safety data from PROWESS. The drug seemed to be relatively safe – with a serious bleeding rate not statistically significantly greater than placebo. Xigris was backed by the highest level of empirical support as an evidence-based-practice. It had editorial support from the NEJM. It had elegant biological plausibility. Over the next ten years, some observational studies seemed to confirm efficacy (2-4), and the drug was determined to be cost-effective (5). Yet even before this supporting evidence began to accumulate, the underpinnings of PROWESS began to unravel.

The FDA approved Xigris in 2001 – but only for that subgroup of patients with an APACHE II score > 25. We were initially surprised that the FDA would make a decision based on a post-hoc subgroup analysis, but we didn’t initially know about numerous irregularities in the study design of PROWESS (6) that were not reported in the original NEJM publication. These were reviewed by Eli Poulos. Inclusion/exclusion criteria of PROWESS were changed midway through the study, in order to eliminate patients with significant non-sepsis related diseases and increase the power of the study. Sites with lower recruitment were dropped.
from the study. The production process for the drug itself was changed, and it was uncertain whether the agent used at the end of the study was identical to that used at the beginning. Even the placebo was changed. The apparent benefit of Xigris appreciably increased after these protocol changes were made (6,7).

The FDA advisory board deadlocked in a ten-to-ten vote over whether or not to approve the drug, yet moved ahead with provisional approval. The FDA was likely under pressure not to unduly restrict potentially life-saving treatments for the highly publicized illness of sepsis.

Our group began to use Xigris with some trepidation, in order to comply with evidence-based practice. We strictly observed the exclusion criteria used in PROWESS, and APACHE II severity scoring as recommended by the FDA. We found that patients only occasionally met these criteria in our busy ICU.

This caution was widespread, and initial sales of Xigris were no doubt disappointing. Heemesh Seth reviewed an editorial from the NEJM regarding the marketing campaign Eli Lilly subsequently implemented to boost sales (8). Eli Lilly provided a $1.8 million grant to fund a task force on “Values, Ethics and Rationing in Critical Care” reportedly to posit the concept that it was unethical to withhold Xigris from septic patients based on cost considerations. This debate over the “rationing” of Xigris made it to the pages of the Wall Street Journal (Sept 2003). Eli Lilly also provided over 90% of the funding for The Surviving Sepsis Campaign, launched in October 2002 to create guidelines for the treatment of sepsis. Many of the international experts who formulated the recommendations of this group had significant outside financial relationships with Eli Lilly. In the initial publication of the treatment guidelines in 2002, the Surviving Sepsis campaign assigned a higher evidence-rating for Xigris in the treatment of sepsis than it did for antibiotics or intravenous fluids. As subsequent prospective trials began to raise important concerns regarding the safety and efficacy of Xigris (see below), these concerns were repeatedly and conspicuously absent from published recommendations of the Surviving Sepsis campaign. In 2004, Eli Lilly started a program of offering unrestricted grants to institutions for implementing Surviving Sepsis Campaign patient management bundles. Sales of Xigris doubled over this period to greater than $200 million per year.

But over the next three years, clinical trials cast increasing doubt on the efficacy of Xigris – these were reviewed by Suresh Uppsala. The ADDRESS trial was a randomized controlled trial that enrolled 2640 patients with severe sepsis and low risk of mortality (9). It showed no difference in 28-day mortality (17 vs. 18% p=0.3). The ENHANCE trial was an open-label study with no control group that showed that the mortality of patients receiving Xigris for severe sepsis was 25% and that the risk of serious bleeding was 6.5% (10) - almost twice as high as reported in PROWESS. The RESOLVE trial was a randomized controlled trial that enrolled 477 children with severe sepsis and showed no difference in mortality, and a 4.6% risk of intracranial hemorrhage (11).
Our group, and likely many others, had already abandoned use of Xigris long before publication of the PROWESS-SHOCK trial last May. The conclusions were anticlimactic. The trial enrolled 1697 patients with septic shock and randomized them to treatment with Xigris or placebo. Mortality at 28-days was 26.4 vs. 24.2% (p=0.3) (12). The rate of serious bleeding in the treatment group was only about 1%, and not significantly different than the rate in the placebo group. These results were a Godsend to Eli Lilly. Xigris was already dead in the water clinically. The extremely low rate of bleeding in the study is likely to diffuse questions about how many patients might have been harmed by Xigris over the past decade.

The authors of PROWESS-SHOCK explicitly state “We cannot explain the inconsistency between our findings and the reduction in mortality at 28 days that was observed in the PROWESS study.”

But we are owed an explanation.

We have been struggling with how to use this drug beneficially at the bedside for over a decade – now it seems most likely to many of us that it never had any benefit at all. It appears that we have spent upwards of a billion dollars on Xigris. Many of us worry that we may have caused serious harm to our patients by giving the drug. Such risks must sometimes be taken when well-intentioned medical research moves forward in fits-and-starts. But the published account in this case suggests that our patients may have been placed at increased risk for financial gain. Particularly disturbing was the apparent attempt to create guidelines to increase sales. It sounds grandiose to suggest, but I can’t help but wonder why Eli Lilly isn’t being asked to explain this story to a Congressional investigative committee.

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References