Xigris 2011: deja vu all over again?

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> "Those who cannot remember the past are condemned to repeat it"
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> "Scepticism is the chastity of the intellect, and it is shameful to surrender it too soon"
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> — George Santayana (1863–1952)

In February of 1991, what was considered a pivotal article was published in the *New England Journal of Medicine*.[1] The article reported the life-saving effects of Centoxin (nebacumab), an HA-1A human monoclonal antibody against endotoxin in 543 patients with sepsis and presumed gram-negative bacteraemia. Centoxin did not decrease overall mortality, but, among patients with gram-negative bacteraemia, it decreased 28-day mortality from 49% to 30% — a significant improvement. Centoxin did not receive United States Food and Drug Administration approval; the trial used multiple end points without adjustment for multiple comparisons; the company (Centocor Biotech) had access to the interim analysis and consequently modified the end points; and, if the preset end points had not been changed, the difference would not have been significant.[2]

Yet the usual frenzy of hype and hope followed, and worldwide use of Centoxin was substantial, with significant initial financial benefits to Centocor. Concern about the wisdom of such use was raised by Natanson's critical care team at the US National Institutes of Health (NIH).[2] They demonstrated that Centoxin had adverse effects in a canine model of gram-negative bacteraemia, and that the drug failed to alter levels of bacteraemia or endotoxaemia.[2] Two large trials of monoclonal antibodies against endotoxin followed in 1994 and in 1995, and their negative results spelled the end of the Centoxin saga.[3,4]

Many lessons could have been learned from this experience. Some of these lessons might have reasonably included the need to exert caution when evaluating the results of a study sponsored by a pharmaceutical company, where data control and analysis was not fully in the hands of an independent data collection, analysis and publication system; the need to remain sceptical in the presence of implausibly good results; the wisdom of requiring a confirmatory trial before embracing the use of a novel drug with poorly understood mechanisms and no published phase I, IIa or IIb studies; and the need to remain vigilant to the risks of mid-trial changes in protocol or drug manufacturing and/or trial centres.

In light of the Centoxin experience, one might have expected the critical care community to be particularly "critical" when another Centoxin-like drug appeared — but it was not. Ten years later, ironically almost to the month, another pivotal trial (Recombinant Activated Human Protein C Worldwide Evaluation in Severe Sepsis [PROWESS]) was published in the same journal[5] — remarkable deja vu for those of us old enough to remember Centoxin. The new drug, Xigris (drotrecogin alfa) (named in the period when Lilly marketing experts preferred drug names starting with letters from the end of the alphabet, hence Viagra and Zyprexa), was launched in 2001 to the same hype and with even more sophisticated marketing techniques.[6] By late 2005, it had recorded sales of $214.6 million,[6] despite the release of a negative second study,[7] and about $100 million in 2011,[8] despite growing concerns about its efficacy.[6]

If only to confirm the sense of deja vu, the same group at the NIH was once again at the forefront of those concerned.[6] This time, these sceptics were joined by other voices in Europe.[9] Concerns were raised that:

- the second trial was terminated because of futility;
- in that trial, surgical patients with severe sepsis and single-organ failure were more likely to die; that 90-day mortality was not significantly different even in the first trial;
- the original trial[5] may not have been adequately blinded;
- there was an unexpected reduction in do-not-resuscitate (DNR) orders in the Xigris arm after a change of protocol halfway through the study,[5] while the DNR rate remained unchanged for the placebo arm;
- halfway through the trial,[5] 20 sites were removed and 45 new sites added; that the dropped sites showed a negative effect of Xigris but the new ones showed a strong positive effect;
- the trial was stopped on interim analysis;[5] and
- patients aged under 50 years had no benefit,[5] but those between 80 and 90 years of age or with chronic morbidities (common candidates for DNR orders) seemed to do better for the primary 28-day mortality outcome.[9]

The demand for another trial in patients who were most likely to be treated with Xigris (those with septic shock) grew stronger and, finally, continued registration by the European Medicines Agency became contingent upon the conduct of such a trial: PROWESS-SHOCK.[10]

On 25 October 2011, Lilly announced that it was withdrawing Xigris from the market in response to the negative results of the PROWESS-SHOCK trial.[8] As this issue of *Critical Care and Resuscitation* went to press, the only trial-related information available was that mortality was 26.4% with Xigris and 24.2% with placebo, and that serious bleeding occurred in 1.2% of patients with Xigris and 1% of patients with placebo. Although many will be interested in the trial details and much is likely to be learnt from its findings, with the removal of the drug from worldwide markets, the Xigris story is over.

Will the medical, and, in particular, the Australian and New Zealand intensive care community learn from this? We hope and think so. The Australian and New Zealand intensive care community has evolved remarkably during the decade that saw Xigris come and go. Its understanding of the difficulties of designing, conducting, analysing and interpreting randomised controlled trials in critically ill patients has increased markedly, and is likely to continue to progress in the coming decade. Pharmaceutical trials will be viewed with much greater scrutiny

and understanding. Convincing animal studies, encouraging phase I investigations, positive phase II work with evidence of benefits using surrogate markers, and at least two independent confirmatory phase II trials will increasingly be demanded before costly experimental treatments are implemented in daily clinical practice.

In the immortal words of Oscar Wilde, "the truth is rarely pure and never simple". A good dose of scepticism is advisable, and Wilde's words should surely serve as a useful mantra in medicine, and justify the future careful and reflective intellectual stance that the saga of Centoxin and Xigris demands of us all.

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