Restored credibility for sepsis therapeutics?

The pivotal phase III clinical trial of one of the last "surviving" sepsis drugs—for the treatment of meningococcal sepsis—is nearing completion. XOMA Corporation's (Berkeley, CA) Neuprex is recombinant human bactericidal/permeability-increasing protein (BPI), an endogenous neutralizer of endotoxin and, with lesser potency, an antibiotic. Some experts are cautiously optimistic about the outcome and hope that positive results will reinvigorate the sepsis field. "This field needs some excitement," says Brett Giroir, of Southwestern Medical Center in Dallas, TX, who is the principal investigator of the Neuprex trial. "If positive, this study is going to answer a lot of questions."

Giroir: BPI is clearly the most effective endotoxin-neutralizing agent available.

There is currently no approved therapeutic for sepsis, the systemic inflammatory response syndrome that afflicts over 80,000 US patients per year and has a mortality rate in excess of 25%. Biotechnology and pharmaceutical companies rushed into that commercial vacuum earlier this decade with inhibitors of a variety of presumed mediators of the sepsis cascade such as endotoxin, interleukin-1, tumor necrosis factor, and bradykinin. Following an extraordinary series of major clinical trial failures by every one of the novel drugs (*Nat. Biotechnol.* **15:**601, 1997), leading clinicians concluded that the biology of sepsis was too poorly understood for anyone to develop a successful therapeutic, and shell-shocked investors stopped funding most research. Ironically, XOMA was sent into total eclipse for several years by the failure of its antiendotoxin antibody, E5.

XOMA avoided calling Neuprex a sepsis drug for a long time, but has begun doing so during the past year, reflecting its growing confidence about the drug's chance of success. The reasons for optimism regarding XOMA's phase III trial, experts say, are based on lessons learned from past failures. All previous sepsis drugs showed activity in at least some retrospectively defined patient subgroups. This suggested that the heterogeneity of patients in "classical" sepsis trials—representing a wide variety of serious, underlying diseases, and probably, as a result, a broad range of serum levels of a drug's biological targets—had confounded efforts to detect the efficacy of the drugs.

In XOMA's phase III trial of Neuprex—expected to include around 300 participants—sepsis patients all have meningococcemia, a bloodstream infection by *Neisseria meningitidis* that occurs in several hundred patients per year. Patients are usually otherwise healthy and all have high levels of endotoxin, Neuprex's target.

Moreover, *Neuprex* differs from previous drugs in that it is a potent neutralizer of endotoxin, whereas the old agents, E5 and Centoxin, were later shown to be relatively weak binders with limited ability to prevent the binding to the next mediator in the cascade. (The inflammatory response seen in many cases of sepsis is produced by human cells when endotoxin, a component of the cell wall of Gram-negative bacteria, is delivered to CD14 by lipopolysaccharide-binding protein [LBP]. BPI works by binding the same site on endotoxin as LBP, thereby inhibiting the endotoxin signal to host cells.) "One hundred percent of patients with meningococcemia are endotoxemic," points out Giroir, adding, "and BPI is clearly the most effective neutralizing agent available."

"I am quite optimistic about this trial," adds Steven Opal, of Brown University (Providence, RI), a leading sepsis researcher who is not involved in the study. "Meningococcemia is perhaps the clinical illness that is most like the endotoxin challenge experiments used in animal labs. If a potent antiendotoxin agent is going to work anywhere in human sepsis, it should work here."

Preliminary clinical data also support optimism. In an earlier 26-patient, open-label, phase I/II trial (*Lancet* **350:**9089, 1997) only one patient (4%) died, compared with 20% in a historical group. In addition, no serious adverse events have been reported in over 700 patients who have received Neuprex in this and other trials.

Full patient enrollment of the phase III trial should be completed by January 1999, and the results unblinded three months later. However, an independent safety and efficacy monitoring committee intends to look at whatever data are complete this month; if strongly positive, the committee could stop the trial on compassionate grounds. Wary Wall Street investors worry this could imply Neuprex's advantage over placebo is marginal so far, and wonder why XOMA has not lined up a large, pharmaceutical company partner for the drug. Skeptics also note that the low incidence of meningococcemia is too small a commercial opportunity to justify the risk of investing in a sepsis drug. XOMA's stock price—near the bottom of its 52-week range—reflects these concerns.

Although XOMA regards the meningococcemia study as proof of concept for the majority of cases in which endotoxin levels are clearly raised, "The utility of BPI as a general antisepsis agent is more problematic, unless we come up with a better way of detecting patients who have an endotoxin-driven illness than we have up to this point," points out Opal.

Addressing the concerns about market size and the potential for more general use, XOMA is currently conducting a 1650-patient, phase III trial in hemorrhagic trauma, in which wounds facilitate the migration of endotoxin-bearing bacteria from the intestinal tract into the bloodstream. In addition, XOMA has developed an assay for LBP—levels of which rise in response to endotoxin—as a rapid test for endotoxin-driven sepsis.

"A positive study in meningococcemia would not just answer questions regarding this disease, it would be the first wedge driven in for doing something for sepsis in general," says Patrick Scannon, XOMA's chief scientific officer.

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