CLINICAL TRIALS

IL-12 Deaths: Explanation and a Puzzle

Researchers testing a promising new drug called interleukin-12 (IL-12) were stunned last June when several patients suffered severe toxic effects and two died from the treatment. The episode was all the more shocking because the patients, who were suffering from kidney cancer, were given doses that had previously proved tolerable. Now the researchers have figured out what triggered the problem, and they have gotten another surprise: The drug apparently has a unique property that couldn't have been foreseen. Researchers don't fully understand this insidious effect, but the good news is that they now know how to avoid it.

Last June's tragic episode was a serious setback for a potential wonderdrug. Earlier tests had indicated that IL-12, a cytokine or cell-signaling protein that can redirect immune responses, might be a potent treatment for diseases as diverse as cancer, AIDS, and malaria. But these visions were put on hold when Genetics Institute (GI) of Cambridge, Massachusetts, announced that genetically engineered IL-12—a product it is developing with Wyeth-Ayerst—had apparently harmed most of 17 renal cell carcinoma patients taking the drug as part of a multisite clinical trial. The toxicities affected multiple organ systems, and two of the patients had died. GI terminated all IL-12 studies, and the Food and Drug Administration (FDA) put IL-12 on "clinical hold," while company scientists attempted to unravel what had gone wrong.

This week, at an IL-12 meeting in Manhattan sponsored by the New York Academy of Sciences, company scientists plan to reveal their findings. The problems appear to have been triggered by the way doses were administered. In early cancer studies, researchers gave patients various amounts of IL-12 to determine a maximum safe single dose. A few weeks later, after the IL-12 had had time to clear from their systems, the patients were given multiple doses of the cytokine. The kidney cancer patients in the second study, in contrast, received multiple IL-12 doses immediately.

Detailed studies done over the summer in mice and cynomologus monkeys have shown a similar pattern: The animals do not get sick if they are given a single dose of IL-12, a rest period, and then multiple doses, but multiple, high doses of IL-12 are highly toxic if they are given without an initial single dose. (Multiple low doses, however, even without an initial single dose, appear safe.) Apparently, the initial dose imprints a memory on the immune system that allows subsequent high doses to be given without harm, explains John Ryan, vice president of clinical development at GI. "I don't know of anything quite like that," says Jay Siegel, an immunologist at the FDA who has been working with the companies.

One possible explanation for this strange phenomenon involves the most celebrated property of IL-12: its ability to shift the balance of white blood cells known as T helper 1 (T_H1) and T helper 2 (T_H2), which direct different arms of the immune system. The initial dose of IL-12 might rearrange populations of these cells such that the immune system can then tolerate multiple doses of the drug. But for now, scientists familiar with the data are reluctant to speculate on mechanisms.

FDA has seen the data and is satisfied that enough of the mystery has been solved to safely begin trials again: On 18 October it lifted the clinical hold. John Petricciani, VP of regulatory affairs at GI, says the company hopes to restart clinical trials soon in both cancer and HIV. What's more, he expects the findings to open new doors for bench scientists. "It will generate a lot of lab interest in this area," predicts Petricciani. "The biological phenomenon is really interesting."

–Jon Cohen

SCIENCE POLICY

Panel Considers Radical Funding Cuts

Should the U.S. government continue to pay for civilian research and development? Last week that seemingly outrageous question was taken seriously by a group of science administrators from government, industry, and academia who spent a day exploring the potential impact on science of a shrunken federal role. The workshop, convened by the Congressional Research Service (CRS), was a deliberate effort to focus the scientific community on the painful choices that may lie ahead. "We offered provocative models," says one CRS staffer. "We wanted to avoid just tinkering with the system."

The meeting explored four scenarios for science on the road to a balanced federal budget by 2002. The starkest choice is an end to all federal R&D except for a small effort to oversee development of the latest military hardware. The second option would continue spending on environmental cleanup, public health, space, and defense R&D, while the third assumes a cut of up to 50% in federal R&D spending. The fourth scenario proposes tilting the federal budget away from defense and toward civilian activities and from applied to basic research, along with halting support for training scientists.

Workshop participants rejected the first option, which would have handed responsibility for U.S. research to states, universities, and nonprofit organizations and left the federal government as a cheerleader for industrial R&D. "It's pretty outrageous," says one. "We agreed it was completely unviable."

The second model, which would sell off or close about half of the laboratories and centers run by the Defense and Energy departments and the National Aeronautics and Space Administration, also won little support. "I don't think they reflect ideas that are widely discussed," says one participant, Al Teich, science policy director for the American Association for the Advancement of Science (which publishes *Science*). "There may be a few people who hold these views," he says, "but not the congressional leadership" or those lawmakers involved in science issues.

The third approach would exceed the one-third cut to science and technology that Congress called for in this year's budget resolution. This option, which would reduce applied research at the National Institutes of Health by 10% to 20%, end energy supply projects, and commercialize the space shuttle, was seen as an omen by some participants. "A 30% to 50% [overall] cut is going to happen," says Rustum Roy, a professor of solid-state physics at Pennsylvania State University who welcomed CRS's attempt to look at the big picture. "It's a healthy exercise and something scientists have not been willing to do," he says.

The fourth model, although it contains less drastic spending cuts, would change the rules for research universities. "The private sector would be responsible for paying the costs of meeting [their employees'] Ph.D. requirements," according to the document. "Education of Ph.D.s would not be used as a primary justification for increasing federal support for university-based research." At the same time, overhead charges would be lowered and eventually capped at 20%. Funding for basic research would remain flat, while applied research and technology would be cut by 30%.

Some Democratic staffers who attended the workshop complained afterward that the scenarios cater to the views of Republicans on the fringe rather than more moderate elements. But CRS science policy staffer and workshop organizer Michael Davey says the point is to begin debating the merits of federal support for science rather than any details. "This is a wake-up call," he added. Teich agrees, noting that the options "get across the point that there is no more business as usual."

–Andrew Lawler