Researchers and regulators reflect on first gene therapy death

The Recombinant DNA Advisory Committee (RAC), the National Institutes of Health office responsible for public oversight of gene therapy, met on 8–10 December to examine the clinical trial in which Jesse Gelsinger became the first person to die from the experimental technique of gene therapy. The RAC responded to his death by citing numerous changes needed to increase the safety of adenovirus vectors. They also proposed revising RAC guidelines for reporting adverse events related to gene therapy, but failed to reach a consensus about these revisions during the meeting.

Gelsinger was an Arizona teenager who died on 17 September soon after receiving adenovirus-based gene therapy for treatment of partial ornithine transcarbamylase (OTC) deficiency—an X-linked defect of the urea cycle in which nitrogen metabolism is affected, leading to a spectrum of neurological symptoms including seizures and mental retardation. Therapy for the condition relies on alternative substrate administration, but mortality rates with the disease are high.

James M. Wilson

Gelsinger was treated at the Philadelphia-based Institute for Human Gene Therapy, directed by James M. Wilson, and in an auditorium crowded to overflowing, a committee comprising RAC and Food and Drug Administration (FDA) members listened as Wilson and his colleagues laid out a 'warts-and-all' account of the clinical trial that abruptly halted with Gelsinger's death.

The trial treated patients with escalating doses of adenovirus vectors bearing the OTC gene. Wilson reported that although Gelsinger's blood ammonia level had been within trial limits when he enrolled, it was mildly elevated when he was due to receive therapy, with the result that he was given alternate pathway medication to stabilize his ammonia level before he received the experimental treatment. He then received the highest dose of the vector in the trial, but still one that other patients in his cohort had been able to tolerate.

By the next morning, Gelsinger had deteriorated so seriously that he was placed in intensive care. The alternate pathway therapy failed, and by the second evening he was comatose. Doctors improved his condition temporarily, but he developed acute respiratory distress syndrome (ARDS) and died two days later of multiple organ failure due to anoxia. Measurements of inflammatory cytokines suggested that the vector had caused systemic inflammatory response syndrome (SIRS), which is associated with ARDS.

None of the animal experiments before the trial indicated that adenovirus might cause lung problems, and at this time, it remains a mystery why Gelsinger was killed by adenovirus treatment. Investigators are testing several possibilities that might explain his death.

Other inexplicable autopsy findings include a near-total wipeout of erythroid precursor cells from Gelsinger's bone marrow, and the puzzle of biodistribution of the adenovirus vector, which was injected into a hepatic blood vessel to reach the liver but which was found in other organs.

Wilson and his colleagues apologized publicly for several mistakes made during the trial. These included failure to inform RAC of a change in protocol, failure to make timely reports to FDA of some animal experiments and failure to report a grade III (serious) adverse response to therapy.

However, FDA documents indicated an extensive, and apparently effective, record of communication between the clinical trial managers and FDA overall. This suggests that the mistakes were unintentional oversights, a view that has been endorsed by leading gene therapy researcher French Anderson. The lack of criticism from RAC members also suggests that many of them share Anderson's opinion.

Anderson believes that early-generation vectors like the one Gelsinger received are now likely to be phased out for most diseases. Gene therapy researchers could turn instead to Merck & Co's 'gutless' adenovirus vectors, which cannot reproduce, give much greater gene expression and are far less inflammatory. Testing of 'gutless' vectors in animals is now being completed.

The RAC presented a list of problems that need to be addressed if adenovirus safety is to improve. Chief among them is that no standard exists for measuring adenovirus titers. Because of this, it is uncertain if therapeutic and toxic adenovirus doses measured by different investigators are comparable.

The RAC also called for better assays for measuring transgene expression in cells and tissues, better assessment of immune status before and after dosing, studies of vector biodistribution and better quality controls for vector DNA integrity.

Although stories in the popular press leading up to the conference led some to believe that the meeting would be a bloodbath, frank behind-the-scenes discussions between the research team, the Gelsinger family and the regulators brought a surprising degree of harmony to the proceedings, despite the circumstances. In fact, the openness with which Gelsinger's death was reported contrasts with recent attempts by other gene therapy investigators to keep deaths reported to the RAC confidential. Claudia Mickelson, who chairs the committee, suggested that confusion about the RAC's policy for reporting serious adverse events may have resulted from the group's reorganization in 1997, when its authority to approve gene therapy protocols was turned over to FDA.

The RAC reiterated that rapid reporting of serious adverse events in gene therapy trials is mandatory whenever trials involve investigators or institutions receiving NIH funding for recombinant DNA activities. But it is important to note that reports to the RAC, unlike reports made to FDA, are not considered confidential, and many of those involved in gene therapy research, and backed by commercial companies, argue that this needs to be revised before reporting can improve.

The RAC discussed revising its current guidelines to dispel confusion about the timing and content of reports of serious adverse events. The revisions are expected to define what is meant by a serious adverse event, state how soon it must be reported and require that patient identities and proprietary commercial information be withheld. But there was no consensus on whether all serious adverse events should be reported, or only unexpected ones, or whether investigators should decide for themselves when such events are unrelated to gene therapy. Nor was there agreement about what would be done with the reports. The RAC will continue its discussions of guideline revisions at its next meeting, in March 2000.

Tom Hollon, Bethesda