Contemporary Clinical Trials in Acute Respiratory Distress Syndrome

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A unique conference attended by clinical investigators, basic scientists, representatives of industry, and representatives of the Division of Lung Diseases of the National Heart, Lung and Blood Institute met in Chicago on May 30 and 31, 1991, to review the current state of clinical trials in acute respiratory distress syndrome (ARDS). Today, the treatment of patients with acute RDS remains supportive; the syndrome remains a problem that has defied a satisfactory solution since its description nearly a quarter of a century ago.1,2 The conference was sponsored by the Respiratory Distress Syndrome Foundation,* in conjunction with the Division of Lung Diseases of the National Heart, Lung and Blood Institute.

The first session was a round-table discussion on "Issues and Challenges in the Conduct of Multicenter Clinical Trials." Conceptual topics that generated debate among the conferees included questions of patient outcome and compliance, the possible adverse effects of treatment, acceptable sample sizes for clinical trials, methods of disseminating the results of those trials, and the role that industry and government should play in the support of such clinical trials. The development of centers of excellence for the treatment and study of acute RDS also provoked discussion. Conferences lamented the variability found in policies governing informed consent, caused in part by a lack of communication among the many institutions and local authorities that deal with the problem of acute RDS. Also discussed was the feasibility of gaining consent for patient entry into clinical trials of acute RDS treatment methods through telephone calls to close relatives in cases in which the patient is unable to give such consent. The development of uniform national standards to guide local policies on informed consent was a concept greeted with some enthusiasm. Also discussed at length were methods by which young investigators might be encouraged to participate in clinical research and controlled clinical trials. The difficulty identified by young investigators is that clinical research is not viewed by the academic world in the same light as is research in the basic sciences; those involved in clinical research may fail to be promoted. Clearly, it is necessary for academic health centers to recognize clinical investigation as the equal of basic science research so that young investigators can do clinical work without any loss of academic standing.

The issue of financial support for the large, placebo-controlled clinical trials required to test new therapeutic methods of acute RDS treatment is a particularly pressing question. Although some clinical trials in acute RDS which successfully competed through the peer review process are now under way, it is extremely unlikely that the National Institutes of Health (NIH) can provide all the resources required to support a new series of clinical trials in acute RDS to exploit the new therapies under development. These budgetary restraints may serve to generate creative solutions to the issue of clinical trial funding by encouraging the formation of new relationships

*About the RDS Foundation ... Timothy Cannon’s family was bewildered by his untimely death almost three years ago. Although he had been seriously injured when his car was forced off the road and struck a tree, doctors had assured the family that the 27-year-old had youth on his side and would very likely recover. Twenty-one days later, on July 6, 1988, Timothy died. First, the family grieved; then it began to ask questions. "I wanted to know what happened to Tim," recalled his father, Frank Cannon, president of George-Beech Corporation. Cannon interrogated doctors at Abington Memorial Hospital and called the National Institutes of Health in Bethesda, Maryland. He learned that his son’s lung injuries had developed into a condition known as acute RDS. Members of the Cannon family were astonished to learn that acute RDS claimed more lives than AIDS, but that it rarely made newspaper headlines. They felt they had uncovered an obscure killer in an era of high-tech medicine. The family also learned that there was no charitable trust or nonprofit foundation dedicated to the disease. Thus, the RDS Foundation was born and two years later it had raised substantial funds for education and research. The foundations mailing address is RDS Foundation, PO Box 723, Montgomeryville, PA 18936.

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among academics, industry, and the NIH. The concept of using established NIH procedures as guidelines for consensus conferences on protocol design, peer review, and data management to aid in industry-supported clinical trials should be explored.

The Division of Lung Diseases does have an ongoing program to support basic research and clinical investigation of acute lung injury. The Specialized Centers of Research (SCOR), a program begun in 1977, serves to encourage young clinical investigators.

The second session of the conference focused on various ongoing SCOR-related clinical investigations. The SCOR programs in Seattle and Denver are focusing their attention on the interactions between leukocytes, inflammatory mediators (eg, cytokines), and endothelial cells in the lung and elsewhere. The SCOR center in San Diego is exploiting a particular interest in thromboembolectomy in its studies of acute lung injury produced by ischemia and reperfusion.

The function of arachidonic acid metabolites in acute RDS cases was the topic of the third session of the conference. The topic of cell-cell interactions involving arachidonic acid metabolism, including substrate shunting and transcellular metabolism, was raised as an issue requiring further investigation. The alveolar airspace in patients with acute RDS becomes a complex milieu in which macrophages, neutrophils, and lymphocytes are present, along with a variety of inflammatory mediators. In this environment, the biochemistry of arachidonic acid metabolism is complex and potentially an important determinant of the behavior of phagocytic cells trapped within the airspace following migration out of the circulation. In designing clinical trials of drugs that alter or prevent the production of arachidonic acid metabolites during acute renal failure, the role of cyclo-oxygenase and lipoxygenase products is a matter of prime concern. This issue was discussed both from the perspective of renal vascular responses to eicosanoids and from the perspective of the role of the kidney in drug metabolism and clearance. A report from an ongoing NIH clinical trial of ibuprofen therapy in patients with sepsis syndrome indicates that the anticipated side effects, such as renal insufficiency and gastrointestinal hemorrhage, may not limit the potential efficacy of this drug. Although physiologic trends in this study are encouraging, it is too early in the trial to draw conclusions about the efficacy of the therapy, particularly in the subset of patients who fulfill clinical criteria for the presence of acute RDS.

Deficiency or inactivation of the surfactant at the air-blood interface may be a mechanism that contributes to decreased lung compliance and the failure to gain improved pulmonary function in patients with acute RDS. Surfactant replacement was the topic of a session on strategies and clinical trials. It was pointed out that insufficient attention has been paid to the epithelial barrier in patients with ARDS, and that injuries may be sustained by type I and type II alveolar epithelium. Surfactant replacement studies in animals with acute lung injury have provided mixed results. However, studies using baboons have shown that an artificial surfactant composed of a phospholipid and a recombinant protein can improve pressure volume curves, an index of lung function. There are several different formulations currently being tested in the United States and Japan through human trials involving infants and adults. A bovine-derived surfactant (the Fujiwara formula) is widely used in Japan (and has just been licensed for use in the United States). Two products are currently being tested in the United States: Exosurf has been shown to reduce mortality in premature infants; and another bovine-derived product, Survanta, is being tested in both infants and adults.

Issues yet to be resolved in the design of large-scale trials that study surfactant replacement in acute ARDS are the delivery system used for the surfactant, patient selection criteria, and the appropriate end points for determining efficacy. The delivery system in adult trials may best utilize either endobronchial infusion or aerosolization of the surfactant, while neither the dose nor the dose interval has yet been optimized. Key issues in the design of controlled clinical trials include patient selection, the stratification of patients by initiating injury, the severity of the disease, the presence or absence of multiorgan failure, and rules for management of ventilator and general patient care. Finally, although survival may be considered the ultimate proof of efficacy, accurate physiologic measurements, such as oxygenation, lung volumes, and compliance, could suggest directions for future studies.

A randomized, controlled, prospective clinical trial to compare inverse-ratio ventilation and extracorporeal CO$_2$ removal at very-low-frequency ventilation rates with conventional continuous positive-pressure ventilation and positive end-expiratory pressure (PEEP) is being completed. Unlike a previously performed, uncontrolled European trial, the controlled trial shows identical outcomes thus far in 40 patients. A feature of the current trial was an attempt to address the issue of uniform care for patients enrolled in a controlled clinical investigation utilizing placebos. Computer algorithms were developed to choose respiratory rate, inspiratory-expiratory ratio, peak inflation pressure, and the level of PEEP. Uniformity of care is an important issue that has not been sufficiently studied in the context of clinical trial design. This approach represents a promising beginning in this important area of investigation.
Sepsis and inflammation are phenomena that must be understood and controlled if the mortality rate associated with acute RDS is to be significantly reduced. The topic of the final session was the daily progress being made in the identification of the mediators and modulators of inflammation. In this field, the recent discoveries of cytokines, growth factors, and adhesion proteins that modify the physiology of the immune system and affect the interactions between phagocytic cells and vascular endothelium have provided exciting new possibilities for intervention. Passive immunization with antibodies to the endotoxin associated with Gram-negative bacteria has shown promise by modifying the natural history of sepsis in patients with Gram-negative infection. Laboratory studies in animals suggest that antibodies directed against tumor necrosis factor alpha and/or certain interleukins may also be of therapeutic benefit. In exploring these new developments, clinical scientists must grapple with all of the existing issues of trial design, as well as new issues based on possible immune responses of the patient to antibody therapies.

It is very likely that clinical trials will be developed to test these new therapies in an attempt to reduce the mortality associated with acute ARDS and multiple organ failure. For example, treatment directed at the mediators of inflammation in patients with sepsis may be combined with surfactant replacement in patients who develop acute respiratory failure. Although these combined intervention trials may provide the best opportunity to affect outcome, they also pose serious new challenges for those who design clinical trials and deal with data management.

It was the consensus of the conference organizers that there is now a need for a planning conference on clinical trial design in ARDS. The careful planning of clinical trials is crucial at this time, as industry is developing powerful new tools with potential therapeutic importance. It is also crucial that such a consensus conference be held in a timely manner, before debate on design issues becomes a retrospective analysis of ongoing trials. Perhaps the support for the organization and staging of such a conference can come from the RDS Foundation, the NIH, and appropriate sources within industry in a joint effort to respond to an urgent need.

REFERENCES

3 Petty TL. Acute respiratory distress syndrome (ARDS). Dis Mon 1990; 36:3-58