Clinical Trial Design in Prevention and Treatment of Acute Respiratory Distress Syndrome

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KEYWORDS

• Acute respiratory distress syndrome • Clinical trial design • Prevention • Treatment

KEY POINTS

- Preclinical studies, involving in vitro and in vivo evidence of efficacy and mechanism of action, are an essential first step toward testing a hypothesis, and can usefully inform clinical trial design. However, in vitro models are limited in their complexity, although important genetic and immunologic differences between animals and humans, together with simplistic in vivo acute respiratory distress syndrome (ARDS) models, limit reliable extrapolation to clinical trials. More complex in vitro systems that mimic the alveolar-capillary interface, together with more clinically relevant animal models and human models of ARDS, could increase the reliability of preclinical investigation.
- Observational studies and systematic reviews and meta-analyses can support a potential clinical effect of an intervention, as well as providing important information for clinical trial design, including event rates and standard deviations in treatment or control groups, recruitment and withdrawal rates, and adverse events.
- Inadequate phase 2 trials provide suboptimal information for the decision to move to phase 3 and the design of the phase 3 trials. Larger phase 2 trials are probably indicated to reduce the risk of studying inactive drugs in phase 3 studies. Biomarkers, such as Ang-2 and surfactant proteins, are promising surrogates for phase 2 studies.
- Phase 3 trial design factors that need to be addressed in ARDS include (1) recruitment of insufficient numbers of patients to detect changes in mortality; (2) excessive heterogeneity; and (3) a lack of standardization of outcome measures.

INTRODUCTION

Over the past several decades, the medical community has strived toward the goal of being guided, to the best of our abilities, by evidence-based practice. There is potentially no other field in medicine in which this goal is more important than in critical care, in which there is a high degree of morbidity and mortality; the cost of care in the United States alone approaches 1% of the country's gross domestic product.[1] Few, if any, other specialties have experienced a more complicated history when it comes to applying clinical trial findings to everyday care.

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Acute respiratory distress syndrome (ARDS) represents a recognizable common pattern of acute alveolar-capillary injury in critically ill patients. However, this pathway is triggered by a wide range of primary disease processes. Despite numerous randomized clinical trials aimed at regulating the lung inflammatory response during ARDS,[2] the only proven therapy to consistently reduce mortality is a protective ventilation strategy.[3] Over the last 4 decades since the first description of the syndrome, and despite new insights into disease pathophysiology and clinical trial design, numerous randomized controlled trials (RCTs) of therapies in ARDS have failed to show convincing benefit (eg, nitric oxide, surfactant, corticosteroids, β-agonists).[2]

In response, some have argued that more basic research is required, because there is not enough understanding of the underlying mechanisms of alveolar-capillary barrier dysfunction in ARDS.[4,5] Although this is no doubt true, others have also emphasized the need to better understand the data required to inform and improve the design of RCTs in ARDS.[6,7] The motive to improve study design is simple. Although studies have failed to show effect, lack of proof does not equal lack of effect. Given the ongoing high incidence and mortality of ARDS, and the high cost of developing potential new therapies, the concept that a therapy should fail to be approved simply because it was inadequately studied is an obvious concern. The development of therapeutic agents also has an ethical dimension, if many patients are exposed to a therapy that did not provide a possibility for clinical improvement.

In this article, the focus is on a stepwise approach (Fig. 1) to inform ARDS trial design: preclinical investigation, observational studies and meta-analysis, and phase 2 and 3 trial design, including patient recruitment, heterogeneity, and appropriate outcomes. The review concludes with a short discussion of how a stepwise approach to the evaluation of therapies in ARDS could reduce the likelihood of erroneously dismissing a potentially valuable therapy.

PRECLINICAL EVIDENCE TO INFORM A STUDY

Although much of the focus in ARDS research has been on clinical trial design, including validation of biomarkers and surrogate end points, many preclinical contributions have been made as well. The body of research required before undertaking a phase 3 trial has not been defined adequately.[7] It usually includes basic science discoveries, testing in animal models or human models of disease, as well as evidence from observational studies, phase 1 and 2 studies, and meta-analyses of previous trials. Before embarking on drug trials, pharmaceutical companies and independent investigators conduct extensive preclinical studies. In vitro and in vivo (animal experiments) studies examine preliminary efficacy, toxicity, and pharmacokinetics. Early in vivo testing specifically aims to show safety, which assists investigators to determine whether a candidate drug has

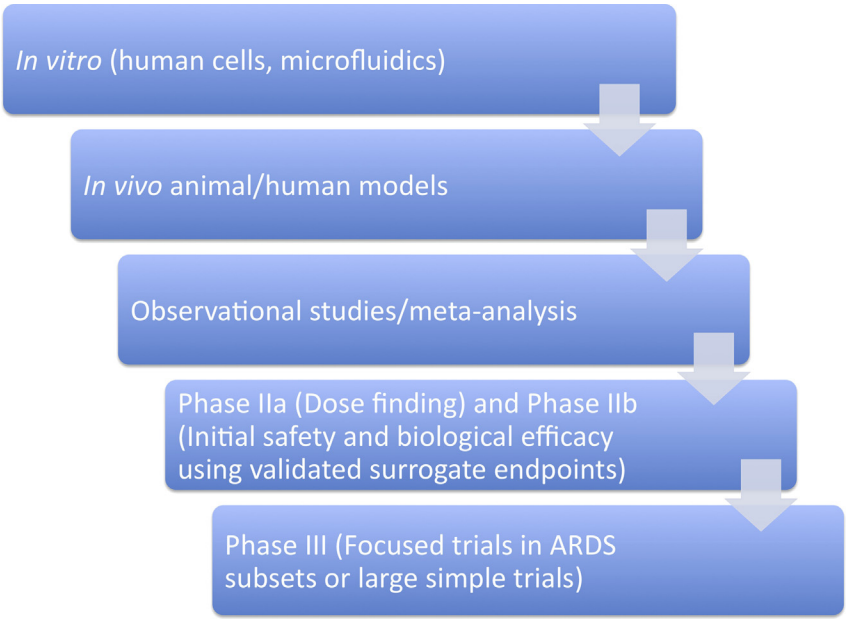

Fig. 1. A stepwise approach in ARDS trial design.