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Therapy for Late-Phase Acute Respiratory Distress Syndrome

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The acute respiratory distress syndrome (ARDS) has arbitrarily been considered as having an early and a late phase. The early phase is characterized by an inflammatory injury with disruption of the alveolar-capillary barrier resulting in leak of protein-rich edema fluid containing neutrophils into the alveolar spaces. The late phase, or so-called ''fibroproliferative'' phase, is characterized by organization and collagen deposition with remodeling [1,2]. The timing of these phases is variable and somewhat arbitrary, in part because of the lack of a large data set of morphology at various points in time in the injury/inflammation/progression/repair process. Recently, the term ''persistent ARDS'' has been used and arbitrarily defined as meeting the criteria for ARDS and requiring mechanical ventilation 7 or more days after onset of the syndrome [3].

Biochemical evidence of fibroproliferation is present early in the injury process. Procollagen peptide III (PIIIP) is a marker of the fibrotic process in a number of disease entities. One study of ARDS found significant levels of PIIIP in bronchoalveolar lavage (BAL) fluid on day 3 following ARDS onset [4]. A subsequent study identified PIIIP in lung edema fluid from patients with ARDS on the first day after onset [5]. The predominant type of collagen deposited in the lungs of victims with ARDS studied at autopsy is type III collagen, interestingly identical to the predominant collagen type in patients with idiopathic pulmonary fibrosis [6]. A marked difference between these two disease syndromes is that the collagen in ARDS survivors presumably clears. There are a few instances with lung morphology to assure this, but studies of pulmonary function in survivors show improvement with return to near-normal to normal levels by 6 to 12 months of follow-up [7,8].

In this article we review the studies of corticosteroid treatment for late ARDS in detail, for this is the only therapy that has been tested by randomized controlled trial in this population. We discuss management and prognosis of patients with late ARDS, and then conclude with an agenda for future research.

History of studies of corticosteroids for early and late acute respiratory distress syndrome

Rationale

The question of whether persistent ARDS with its fibroproliferative predominance warrants different treatment strategies than ARDS at its onset has been a vexing one. At its heart has been the hypothesis that the antifibrotic properties of corticosteroids will benefit patients with persistent ARDS. Presumably, the same or similar argument could be made for corticosteroid treatment of early ARDS based on the anti-inflammatory effects of steroids. Definitive answers have been difficult because of the variety of dose, duration, and tapering strategies and regimens used. The approach that has been best studied is the use of high doses of corticosteroids administered early in ARDS for 1 or 2 days. This regimen does not improve outcomes and may worsen them both in patients with established ARDS [9–11] or in patients at high risk for ARDS (septic shock) [11–13].

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Case series

Corticosteroids were first proposed and systematically administered in patients with persistent ARDS by Ashbaugh and Maier [14]. They performed open lung biopsies in 10 patients both to establish that inflammatory fibrosis was present and to rule out infection. They then administered a prolonged course of moderate doses of corticosteroids as methylprednisolone given intravenously. Eight of these 10 patients survived, a number higher than expected based on overall survival rates for patients with ARDS at that time. This series was followed by publication of several other similar uncontrolled series (although without lung biopsies) with similar overall results; survival was between 70% and 80% [15–19]. This high survival rate was impressive to most ARDS ''experts'' but the expected outcome of patients with persistent ARDS was unknown at the time of publication of these series. We will return to this issue later.

First randomized, controlled trial of corticosteroids for persistent acute respiratory distress syndrome

These encouraging results led Meduri and coworkers [20] to conduct a randomized controlled trial of corticosteroids in patients with persistent ARDS. They randomized patients in a 2:1 ratio to either methylprednisolone or placebo. The dose of methylprednisolone was 2 mg/kg initially, followed by 2 mg/kg/day in divided doses for 14 days, followed by 1 mg/kg/day in divided doses for another 7 days, followed by 0.5 mg/kg/day in divided doses for another 7 days, followed by a final taper over 4 days. The authors considered clinical improvement as being a one-point decrease in the Lung Injury Score at or before 10 days of treatment. The study design included a provision to crossover to the alternative treatment if that criterion for improvement was not met by 10 days.

Twenty-four patients were included in the study. All 16 patients in the steroid-treated group met the criterion for clinical improvement, whereas only 2 of the 8 patients randomized to placebo improved. However, four of the patients randomized to placebo were subsequently treated with corticosteroids under the crossover scheme; the other two unimproved patients died before crossover. The intention-to-treat analysis demonstrated that randomization to corticosteroids was associated with a statistically significant improvement in survival. This survival benefit was no longer statistically significant, however, if analyzed by actual treatment (comparing the outcome of the 20 subjects who received corticosteroids with the 4 subjects who did not).

This study and its results were controversial based on its small size and unconventional methodology, including multiple interim analyses and the use of the crossover design, which made survival difficult to interpret. Nonetheless, the clear demonstration of clinical improvement by day 10 was certainly encouraging.

National Institutes of Health National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network study of corticosteroids for persistent acute respiratory distress syndrome

Study design

Based on these favorable but uncertain outcomes, the National Institutes of Health–sponsored National Heart, Lung, and Blood Institute ARDS Clinical Trials Network (ARDSnet) decided to conduct a trial of corticosteroids in patients with persistent ARDS, defined as meeting ARDS criteria with continuous need for endotracheal intubation and mechanical ventilation for at least 7 days and no more than 28 days after the onset of ARDS [3]. Corticosteroid administration was similar to the regimen used by Meduri and colleagues [20], but with a few differences. The regimens were identical for the first 21 days. Meduri and coworkers continued treatment for 28 days before beginning a taper; the ARDSnet study began tapering corticosteroids on study day 21. The final taper of both studies occurred over 4 days: study days 29 to 32 in the Meduri protocol, study days 22 to 26 in the ARDSnet protocol. Additionally, subjects who achieved 48 hours of unassisted breathing were rapidly tapered in the ARDSnet protocol, but not in the Meduri protocol.

The primary outcome variable in the ARDSnet study was mortality 60 days after study entry. Since enrollment was slow over the first 2 years, the study was re-sized to detect a 20% decrease in mortality (40% to 20%) with 85% power and a two-sided significance of 5%. It took 7 years for 10 university centers to enroll the required 180 patients, a finding that may suggest that patients meeting this definition of persistent ARDS are less common than initially suspected. It is possible that current treatment of ARDS, especially lung-protective ventilation, has decreased the