CORRESPONDENCE

Corticosteroids in ARDS

TO THE EDITOR: The controlled trial of the use of corticosteroids in the acute respiratory distress syndrome (ARDS) by the National Heart, Lung, and Blood Institute (NHLBI) ARDS Clinical Trials Network (April 20 issue)[1] has limitations that affect the interpretability of the results. First, since only 180 of 3464 eligible patients (5 percent) were enrolled, the study population was not representative of those typically seen in clinical practice. Second, recent data demonstrate that patients with ARDS have excessive activation of nuclear factor-κB, with excessive production of proinflammatory cytokines.[2] This imbalance between the proinflammatory and antiinflammatory responses is present from the outset of this disorder, and it is therefore counterintuitive to delay treatment with corticosteroids until day 7. For example, a recent single-center trial demonstrated a benefit in terms of the length of stay and survival when corticosteroids were started on day 1.[3]

Third, in the trial, high doses of corticosteroids (according to our estimates, an average of 150 mg of methylprednisolone per day) were administered and stopped abruptly on extubation. This oversight in trial design may have led to the observed result. High-dose corticosteroids are associated with myopathy; furthermore, without tapering, there could have been corticosteroid insufficiency. These factors most likely contributed to the high rate of reintubation in the corticosteroid group (20 patients, vs. 6 patients in the placebo group), in light of data showing a rebound in proinflammatory cytokines, with resulting clinical deterioration, when corticosteroids are abruptly stopped.[4]

We recognize that many of these methodologic issues are related to the fact that this study was designed in the mid-1990s. Furthermore, although most secondary end points were improved by treatment with corticosteroids, the lack of benefit with respect to survival is at least partly due to a lack of statistical power. The results of this trial reinforce the need for further prospective studies based on the current thinking of the basic science, pathogenesis, and pathophysiology of ARDS, as well as our understanding of the role of glucocorticoids in modulating the inflammatory response.

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THIS WEEK'S LETTERS

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TO THE EDITOR: The fact that despite improvement in physiological variables, corticosteroids did not improve the outcome of persistent ARDS in the NHLBI ARDS Clinical Trials Network study is counterintuitive. We suggest two potential confounding factors. First, the active-treatment group included considerably more women. It has been demonstrated, however, that owing to sex differences in hepatic cytochrome P-450 metabolism, the area under the curve of methylprednisolone for women is only 68 percent of that for men.[1] This might have been the reason that in our case–control study, significantly more women who were treated with corticosteroids did not have a response to therapy and died.[2] Thus, it might be of interest to know whether there were any sex-based differences with respect to outcome in the present study.

Second, there is evidence from prior studies in animals[3] and clinical studies[2,4] that the premature discontinuation of corticosteroids may be associated with secondary deterioration in lung function that can be resolved by the reinstitution of treatment. In the NHLBI ARDS Clinical Trials Network study, however, there was no mention of such cases or of any rescue corticosteroid treatments.

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TO THE EDITOR: The NHLBI ARDS Clinical Trials Network study clearly and reasonably demonstrates that the routine use of methylprednisolone for persistent ARDS does not lead to a better outcome than the use of placebo and that starting methylprednisolone therapy more than two weeks after the onset of ARDS increases the risk of death. Persistent ARDS is characterized by extensive tissue inflammation; this is the main reason for the use of corticosteroids for this fatal disorder.[1,2] In a study of corticosteroid-resistant bronchial asthma, the ligand-binding and DNA-binding affinity of the glucocorticoid receptor were diminished in patients who had resistance to corticosteroids as a result of poorly controlled inflammation, which was potentially triggered by certain cytokines.[3] In addition, one report showed that prolonged inflammation induces a high level of expression of transcription factor AP-1 and that this molecule competes for the DNA-binding site of the glucocorticoid receptor, resulting in corticosteroid resistance.[4] Thus, in patients who started therapy more than two weeks after the onset of ARDS, a corticosteroid-resistant state may already be established, methylprednisolone may no longer be effective, and its side effects may surpass its antiinflammatory effects.

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TO THE EDITOR: The success of treatment of established ARDS, whether in its early exudative or later fibroproliferative stages, has been disappointing. Preemptive therapy may be a more fruitful approach, but it would require the reliable identification of impending ARDS on the grounds of clinical and laboratory findings. Gelsolin is a multifunctional protein normally circulating in human plasma. The depletion of plasma gelsolin precedes and predicts the subsequent development of acute lung injury in many common clinical circumstances, including after major trauma and transplantation.[1,2] Gelsolin decreases the viscosity of air-

way secretions in patients with cystic fibrosis and asthma while potentiating the bactericidal activity of cationic endogenous antimicrobial peptides and exogenous antibiotics. Appropriately timed infusions of recombinant human gelsolin can abolish evolving lung injury in animal models of hyperoxia, burns, and sepsis.[3,4] A particular advantage of gelsolin therapy derives from its modulation of multiple overzealous and potentially injurious host responses to diverse insults. Gelsolin also inhibits certain actions of bacterial endotoxin.[5] Physiologic gelsolin repletion in patients at substantial risk for ARDS with markedly reduced gelsolin levels may provide a direct and effective therapeutic intervention.

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Dr. DiNubile reports being employed by Merck.

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THE AUTHORS REPLY: Our hypothesis was that moderate-dose corticosteroids would improve survival among patients with persistent ARDS, as previously reported.[1] We were unable to demonstrate that effect. Marik and colleagues raise a different hypothesis regarding early-phase ARDS, one that may be worthy of study despite negative results with high-dose, short-course corticosteroids in previous clinical trials.[2,3]

Our results were disappointing but not counterintuitive. Drugs have benefits that can be offset by unintended adverse effects. Improved physiology does not necessarily result in improved survival, as observed with inhaled nitric oxide and surfactant replacement, for example.[4,5]

As noted, we had an imbalance in the percentage of men at randomization. The interactions between sex and treatment with regard to 60-day mortality and the number of ventilator-free days were not significant (P=0.41 and P=0.22, respectively).

Few efficacy trials are unconditionally generalizable, yet a low ratio of enrolled to screened patients, seen in many large clinical trials dealing with critical care, does not necessarily preclude generalizability. Our enrolled patients were quite sick, according to the baseline severity of measures of illness, and they reflected the population we wanted to study. The baseline Lung Injury Scores and ratios of the partial pressure of arterial oxygen to the fraction of inspired oxygen were nearly identical to those in the prior trial.[1]

Our study used a regimen of moderate-dose corticosteroids that was very similar to one studied previously, though our duration of treatment was shorter.[1] We did not use a crossover design, nor did we allow for rescue therapy, on the basis of our equipoise regarding corticosteroids. We did not stop corticosteroids "abruptly"; we tapered the dose over a period of six days, since patients had to have two days of unassisted breathing before the four-day taper began. Was this long enough? Could a rebound effect be operative? We recognized these possible explanations and discussed them in our article. There are many potential causes for the need to resume mechanical ventilation, including neuromyopathy. The possibility that recurrent, sterile inflammation was present and would again be responsive to corticosteroids well into the first month of ARDS would require further study, perhaps guided by biomarkers of lung inflammation and fibrosis.

Our trial was powered to detect a signal 60 percent smaller than that previously described.[1] We agree it is possible that a small treatment effect was missed. Nearly 1000 patients would need to be enrolled to confirm a 10 percent survival benefit for the subgroup enrolled less than 14 days after the onset of ARDS.

The gelsolin hypothesis is appealing. We do not know whether a corticosteroid-resistant state explains the results in the subgroup enrolled between 14 and 28 days after the onset of ARDS, but that subgroup was small, albeit predetermined. Such analyses should be interpreted with caution.

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Lung Recruitment in Patients with ARDS

TO THE EDITOR: In the April 27 issue, Gattinoni et al.[1] suggest that the potential for lung recruitment in patients with acute lung injury is generally low and extremely variable among patients. We believe that a suboptimal recruitment maneuver explains such results, contradicting investiga-

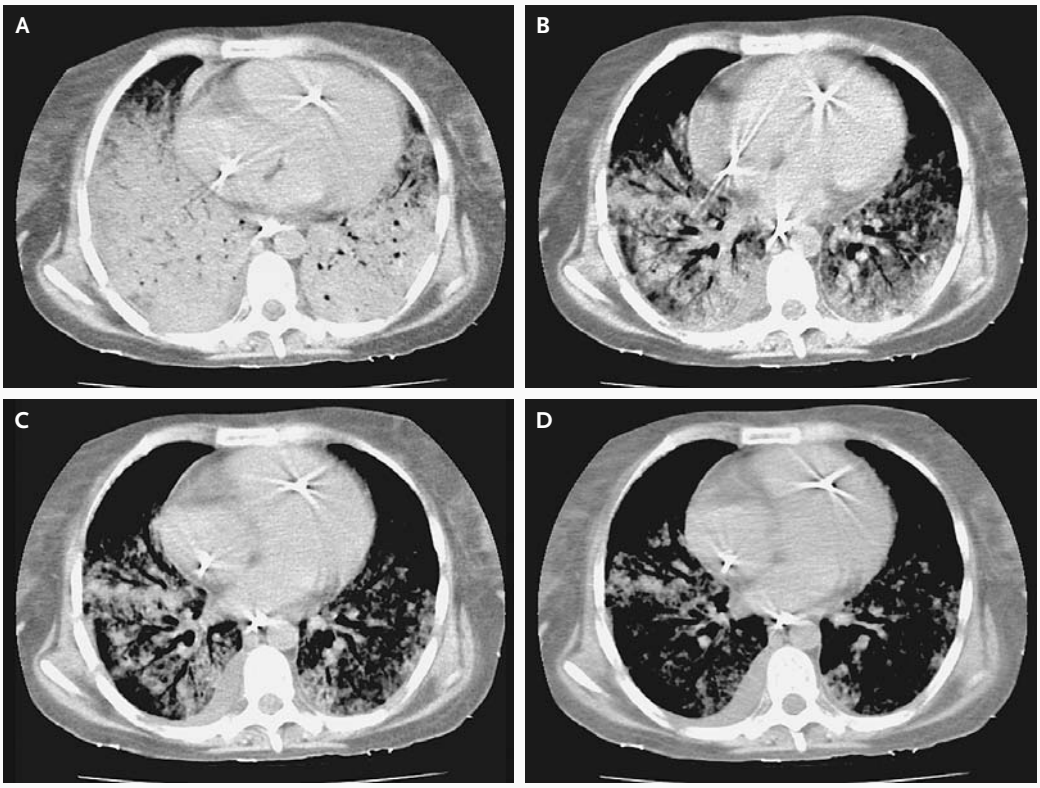

Figure 1. Computed Tomographic Images Obtained at the End-Expiratory Pause in a Patient with Pneumocystosis and the Acute Respiratory Distress Syndrome.

The images were obtained under different ventilatory conditions: a positive end-expiratory pressure (PEEP) of 5 cm of water and a plateau pressure of 20 cm of water (Panel A), a PEEP of 17 cm of water and a plateau pressure of 40 cm of water (Panel B, similar to the strategy used by Gattinoni et al.), a PEEP of 25 cm of water and a plateau pressure of 40 cm of water (Panel C), and a PEEP of 25 cm of water and a plateau pressure of 60 cm of water (Panel D). The corresponding potential for recruitment (relative to the conditions in Panel A) was 35 percent for the conditions in Panel B, 67 percent for the conditions in Panel C, and 87 percent for the conditions in Panel D. At the same plateau pressures (Panels B and C), the application of a higher PEEP (25 cm of water in Panel C) improved the efficacy of the maneuver. A further increase in inspiratory plateau pressure (Panel D) revealed the full potential for recruitment.