

## EDITORIALS



## Lung Inflammation in ARDS — Friend or Foe?

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There is good reason that treatment of the acute respiratory distress syndrome (ARDS) with corticosteroids has been a much-studied subject. In response to a number of serious underlying events, such as sepsis, inhalation of gastric contents, and multiple trauma, the body reacts with acute inflammation of the lung parenchyma — a process that is characterized by increased vascular permeability, extravasation of plasma, and leukocyte infiltration; this combination of events is known as ARDS. This illness has an early acute phase that affects all patients; a variable fraction have a late phase, characterized by pulmonary fibrosis. Management of either phase of ARDS is particularly challenging because the hypoxemia is frequently life-threatening and no effective drug therapy is available.<sup>1</sup>

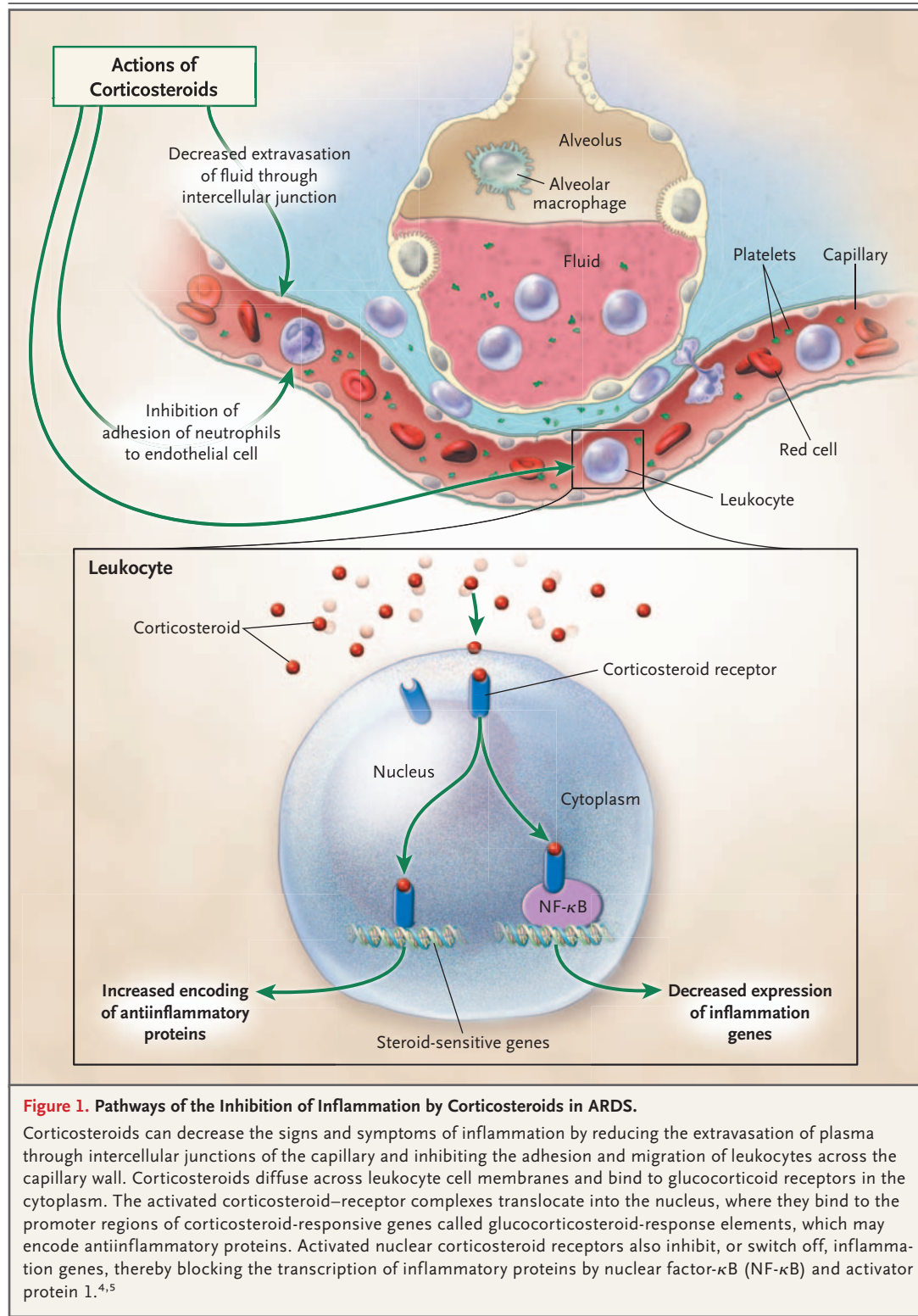
Treatment of the acute phase of ARDS with corticosteroids has been disappointing,<sup>2</sup> but corticosteroid administration in late ARDS (more than seven days after its onset) has been more promising.<sup>3</sup> However, treatment is limited by the potential side effects of corticosteroids, such as prolonged neuromuscular weakness, superinfection, and sepsis.

Why even consider corticosteroids in late-phase ARDS? Corticosteroids exert strong antiinflammatory action by means of effects on multiple signaling pathways at the intracellular level and on membrane-associated receptors by way of non-transcriptional pathways (Fig. 1). They can switch off genes activated during the inflammatory process — genes responsible for the synthesis of proinflammatory proteins, such as cytokines, chemokines, adhesion molecules, inflammatory enzymes, and receptors. Genes encoding antiinflammatory mediators, including interleukin-10, the inhibitor of nuclear factor- $\kappa$ B, and interleukin-1-receptor antagonist, are switched on by cor-

ticosteroids.<sup>4,5</sup> The extensive tissue inflammation observed in ARDS would appear to be a promising target for corticosteroids. As a result of decreasing inflammation in the lung parenchyma, improvement in markedly impaired pulmonary gas exchange may be achieved.<sup>3</sup> This effect could allow physicians to use lower inspiratory oxygen concentrations and to avoid the high tidal volumes and elevated lung-distending pressures that may cause additional lung injury and lead to decreased survival.<sup>6,7</sup>

In this issue of the *Journal*, investigators from the ARDS Clinical Trials Network, sponsored by the National Heart, Lung, and Blood Institute, report on a multicenter, randomized trial of corticosteroid treatment in 180 patients with ARDS<sup>8</sup>; no survival benefit was noted at 60 and 180 days after enrollment, when corticosteroids were administered to patients with ARDS persisting beyond 7 days. However, corticosteroids led to better outcomes than placebo with respect to a number of secondary end points, including an increased number of ventilator-free days by day 28, improved arterial oxygenation, increased respiratory compliance, and a lower incidence of pneumonia and septic shock. In the subgroup in which corticosteroid administration was begun 7 to 13 days after the onset of ARDS, 60-day and 180-day mortality was 25 percent lower in the corticosteroid group than in the placebo group, but this difference did not reach statistical significance. However, among patients who began receiving corticosteroids 2 or more weeks after the onset of ARDS, there was a significant cost: mortality was four times that in the placebo group at 60 days. In addition, persistent muscular weakness was more frequent among patients treated with corticosteroids.

This clinical trial clearly indicates that cortico-



steroid therapy does not provide a better outcome in ARDS, but it also raises certain questions. There are simple questions, such as this: Can we be sure that during the course of the study — more than six years — there were no significant changes in the care of these patients that could have influenced outcome? For example, avoidance of high tidal volumes and airway pressures is now an accepted therapeutic approach, but this understanding evolved over the period the study was conducted.<sup>6,7</sup> Would the results have been different with other corticosteroid-treatment schedules?

However, the critical question is the following: By what biologic mechanism can corticosteroids provide beneficial pulmonary and cardiovascular effects when given after seven days in patients with persistent ARDS but increase mortality when started at later stages? One hypothesis is that inhibition of the inflammatory response in very early phases as well as in late phases interferes negatively with physiologic defense and repair mechanisms, which are enhanced by inflammation. This hypothesis is based on the idea that the balance between the beneficial and detrimental effects of inflammation, and of its inhibition by corticosteroids, is different in various phases of ARDS. This concept is not necessarily limited to a single organ but, rather, must involve the systemic effects of lung inflammation.<sup>9</sup> There is evidence that corticosteroids not only have a beneficial effect on tissue defense and repair mechanisms but also prompt a systemic immunosuppressive response.<sup>10</sup> This idea suggests that immunomodulation of pulmonary inflammatory defense mechanisms should ideally be balanced to avert broad systemic immunosuppression and interference with physiologic signaling. In this way, improved lung function could be associated with limitation of infectious complications — two essential ingredients for a better outcome. A potential time frame for corticosteroid therapy in ARDS, as well as the optimal regimen, remains to be defined, but the current study suggests that there is a narrow window of opportunity — between 7 and 14 days after the onset of the disease — in which cardiopulmonary function and possibly outcome may be improved.<sup>8</sup>

In conclusion, routine administration of corticosteroids in ARDS cannot be recommended today, and their use seems harmful when started

two weeks or more after onset. Clinical research must continue in this area to enhance our understanding of basic mechanisms of lung injury, physiologic defense mechanisms, and tissue repair. Because inflammation plays a central role in the mechanisms of this disease, therapies to modulate its detrimental effect without suppressing its beneficial actions may decrease the high mortality among patients with ARDS. It is certainly an illusion to believe that proinflammatory and antiinflammatory processes happen at similar time points in all patients. The time course of these processes may vary — not only because of the complexity of the disease, but also possibly because of differences in genetic background and individual susceptibility. More precise monitoring methods to assess pulmonary and systemic immune-response status are probably necessary to determine the optimal time of intervention. It is hoped that progress in this field will add to the survival benefits provided by other essential components of intensive care management in these patients, including nonaggressive ventilatory support and appropriate and timely antimicrobial therapy, in concert with the many other effective treatments provided in today's intensive care units. It is the hallmark of important investigations such as the current ARDS Clinical Trials Network study that they provide not only interesting data, but also stimulating new questions for future research.

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## Pharmacotherapy for Prehypertension — Mission Accomplished?

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Prehypertension, defined as the blood-pressure range of 120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic, is present in about 70 million Americans.<sup>1,2</sup> The condition heralds arterial hypertension and thus may be considered a starting point in the cardiovascular disease continuum. Because of its high prevalence and long-term complications, prehypertension has been estimated to decrease the average life expectancy by as much as five years.<sup>3-5</sup> Unfortunately, current preventive strategies, although admirable from both individual and societal perspectives, are weak.

In this issue of the *Journal*, the investigators of the Trial of Preventing Hypertension (TROPHY) present data from a study of pharmacologic intervention for the prevention of hypertension.<sup>6</sup> In their report, Julius and colleagues propose that inhibition of the renin-angiotensin system in persons with prehypertension may interfere with a self-accelerating process leading to hypertension and, ultimately, target-organ damage. Indeed, in young rats with spontaneous hypertension, in a model of essential hypertension, angiotensin-converting-enzyme inhibitors delayed the onset of hypertension far beyond the active treatment period.<sup>7</sup>

In the TROPHY study, 772 participants with blood pressures in the range of 130 to 139 mm Hg systolic or 85 to 89 mm Hg diastolic, or both — that is, in the upper half of the spectrum defined as prehypertensive — were treated for two years with either the angiotensin-receptor blocker candesartan or placebo (the first phase of the study).<sup>6</sup> The two groups then received placebo for an additional two years (second phase). The end point, stage 1 hypertension, was reached in most cases when a single blood pressure reading at a clinic visit was higher than 159/99 mm Hg or

when readings on three clinic visits, averaged, were higher than 139 mm Hg systolic or 89 mm Hg diastolic.

Two years after active treatment had been stopped, hypertension was observed less frequently among participants in the candesartan group than among those in the placebo group. Specifically, transient treatment with an angiotensin-receptor blocker was subsequently related to a significant absolute difference of 9.8 percent between the two groups and a relative risk reduction of 15.6 percent for the development of hypertension at the end of the four-year study. Moreover, there were slightly lower blood-pressure readings and fewer participants receiving antihypertensive medication among those formerly in the candesartan group. The authors conclude that administering an angiotensin-receptor blocker for two years postponed the manifestation of stage 1 arterial hypertension for a prolonged period.<sup>6</sup>

A number of scientific implications may be inferred from these results. Chiefly, medical treatment of prehypertension does not simply mask the subsequent development of overt hypertension. Rather, important effects can be observed, even if treatment with an angiotensin-receptor blocker is followed by a long period of placebo “washout.” Thus, these investigators successfully tested the hypothesis that prehypertensive levels of blood pressure and the intimately involved renin-angiotensin system, together or separately, are key players in a vicious circle that ultimately leads to new-onset hypertension.

However, some of the study data should be interpreted with caution. In epidemiologic studies, by definition, the need for medical treatment with antihypertensive agents such as candesartan would fulfill the criteria for arterial hyper-