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AMERICAN COLLEGE OF CHEST PHYSICIANS®

Methylprednisolone Infusion in Early Severe ARDS*

Results of a Randomized Controlled Trial

G. Umberto Meduri, MD, FCCP; Emmel Golden, MD;
Amado X. Freire, MD, MPH, FCCP; Edwin Taylor, MD;
Muhammad Zaman, MD; Stephanie J. Carson, RN; Mary Gibson, RN; and
Reba Umberger, RN, MS

Objective: To determine the effects of low-dose prolonged methylprednisolone infusion on lung function in patients with early severe ARDS.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: ICUs of five hospitals in Memphis.

Participants: Ninety-one patients with severe early ARDS ($\leq$ 72 h), 66% with sepsis.

Interventions: Patients were randomized (2:1 fashion) to methylprednisolone infusion (1 mg/kg/d) vs placebo. The duration of treatment was up to 28 days. Infection surveillance and avoidance of paralysis were integral components of the protocol.

Main outcome measure: The predefined primary end point was a 1-point reduction in lung injury score (LIS) or successful extubation by day 7.

Results: In intention-to-treat analysis, the response of the two groups (63 treated and 28 control) clearly diverged by day 7, with twice the proportion of treated patients achieving a 1-point reduction in LIS (69.8% vs 35.7%; p = 0.002) and breathing without assistance (53.9% vs 25.0%; p = 0.01). Treated patients had significant reduction in C-reactive protein levels, and by day 7 had lower LIS and multiple organ dysfunction syndrome scores. Treatment was associated with a reduction in the duration of mechanical ventilation (p = 0.002), ICU stay (p = 0.007), and ICU mortality (20.6% vs 42.9%; p = 0.03). Treated patients had a lower rate of infections (p = 0.0002), and infection surveillance identified 56% of nosocomial infections in patients without fever.

Conclusions: Methylprednisolone-induced down-regulation of systemic inflammation was associated with significant improvement in pulmonary and extrapulmonary organ dysfunction and reduction in duration of mechanical ventilation and ICU length of stay.

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Key words: ARDS; duration of mechanical ventilation; glucocorticoid treatment; infections; systemic inflammation

Abbreviations: APACHE = acute physiology and chronic health evaluation; F_{IO_2} = fraction of inspired oxygen; LIS = lung injury score; MODS = multiple organ dysfunction syndrome; PEEP = positive end-expiratory pressure

In ARDS, the evolution of systemic and pulmonary inflammation in the first week of mechanical ventilation determines the physiologic progression (resolving vs unresolving) and outcome of the disease.[1–3] The lung injury score (LIS) quantifies the physiologic respiratory impairment in ARDS through the use of a 4-point score based on the levels of positive end-expiratory pressure (PEEP), ratios of PaO_2 to fraction of inspired oxygen (F_{IO_2}), the static lung compliance, and the degree of infiltration present on chest radiograph.[4] Patients failing to improve the LIS or its components by day 7 of

ARDS (unresolving ARDS), contrary to improvers, have persistent elevation in circulating and BAL levels of inflammatory cytokines and chemokines, markers of alveolocapillary membrane permeability and fibrogenesis (dysregulated systemic inflammation),[1–3] and a higher mortality.[5–7]

We have previously shown[1,2,8] that systemic inflammation-induced glucocorticoid receptor resistance and/or insensitivity is an acquired, generalized process central to the pathogenesis of unresolving ARDS that is potentially reversed by quantitatively adequate and prolonged glucocorticoid supplemen-

tation. In a small randomized trial,[2,8–10] prolonged methylprednisolone administration (2 mg/kg/d) initiated in nonimprovers after 9 ± 3 days of ARDS onset was associated with rapid, progressive, and sustained reductions in plasma and BAL inflammatory cytokines, chemokines, and procollagen levels

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with parallel significant improvement in lung injury and multiple organ dysfunction syndrome (MODS) scores. Treatment was associated with a significant reduction in duration of mechanical ventilation and ICU mortality.[9] Three additional randomized trials[11–13] investigating prolonged glucocorticoid treatment in acute lung injury and ARDS were published showing a significant reduction in levels of inflammatory markers and duration of mechanical ventilation.

Since the direction of the systemic inflammatory response (regulated vs dysregulated) is established early in the course of the disease,[1,2] we tested the hypothesis that prolonged administration of low-dose methylprednisolone (1 mg/kg/d) initiated in early ARDS (within 72 h of diagnosis) downregulates systemic inflammation and leads to earlier resolution of pulmonary organ dysfunction and a reduction in duration of mechanical ventilation and ICU stay. The present trial substantially differs from a prior study with negative findings that investigated, in 100 patients with early ARDS, a 1-day treatment with high-dose (120 mg/kg) methylprednisolone.[6] Preliminary results of the per-protocol analysis of this study have been reported in abstract form.[14,15]

Materials and Methods

Patients

This investigation was conducted between April 1997 and April 2002 in the medical and surgical ICUs of Baptist Memorial

*From the Memphis Lung Research Program (Dr. Meduri, Ms. Carson, Ms. Gibson, and Ms. Umberger), Baptist Memorial Hospital (Dr. Golden), Regional Medical Center (Dr. Freire), the Veterans Affairs Medical Center Memphis (Dr. Zaman), and St. Francis Hospital (Dr. Taylor), Memphis, TN.
Correspondence to: G. Umberto Meduri, MD, FCCP, Division of Pulmonary Division of Pulmonary, Critical Care, and Sleep Medicine, University of Tennessee Health Science Center, 956 Court Ave, Room H316, Memphis, TN 38163; e-mail: umeduri@utmem.edu

Medical Center and East Hospitals, the Regional Medical Center, St. Francis Hospital, University of Tennessee Bowld Medical Center, and the Veterans Affairs Medical Center, all in Memphis, TN. Each institutional review board approved the study protocol, and informed consent was obtained from patients or their legally authorized representative prior to enrollment. Adult intubated patients receiving mechanical ventilation were eligible if, within 72 h of study entry, they met diagnostic criteria for ARDS by the American-European Consensus definition[16] while receiving PEEP. Exclusion and exit criteria are reported in the *CHEST* Web-based repository.

Testing of Adrenal Function

At randomization, function of the hypothalamic-pituitary-adrenal axis was assessed with a short cosyntropin stimulation test. Blood was collected for a basal cortisol level; a 250-μg bolus of cosyntropin (Organon Corporation; West Orange, NJ) was administered by IV push, followed by blood collection for cortisol at 60 min. A central laboratory performed cortisol measurements by fluorescence polarization immunoassay (TDx instrument; Abbott Laboratories Diagnostic Division; Abbott Park, IL) using Abbott reagents. The sensitivity of the assay was 0.45 μg/dL. Relative adrenal insufficiency was defined by a cosyntropin-stimulated total cortisol increment < 9 μg/dL or, in the absence of stimulation, by a baseline cortisol level < 15 μg/dL.[17]

Treatment Protocol

The 2:1 randomization protocol is reported in the Web repository. Although a 1:1 randomization design requires fewer patients for the same effect and power than a 2:1 randomization design, the latter is useful to gain knowledge with the response (positive and negative) to a new treatment application. Methylprednisolone or normal saline solution placebo was mixed in 240 mL of normal saline solution and administered daily as an infusion at 10 mL/h and changed to a single oral dose when enteral intake was restored. A loading dose of 1 mg/kg was followed by an infusion of 1 mg/kg/d from day 1 to day 14, 0.5 mg/kg/d from day 15 to day 21, 0.25 mg/kg/d from day 22 to day 25, and 0.125 mg/kg/d from day 26 to day 28. If the patient was extubated between days 1 and 14, the patient was advanced to day 15 of drug therapy and tapered according to schedule.

Ventilator management guidelines were initially designed to limit plateau pressure at ≤ 35 cm H_2O[18] and were later changed to conform with the ARDSnet findings.[19] Unless contraindicated, diagnostic fiberoptic bronchoscopy with bilateral BAL was performed prior to study entry, and then every 5 to 7 days.[20] Methodology for BAL and processing of distal respiratory secretions followed established guidelines.[21]

In conformity with ethical principles that guide clinical critical care research (reviewed by Luce et al[22]), we incorporated steps into the protocol (reported in the Web repository) to maximize benefits and to minimize risks (prevent complications associated with glucocorticoid treatment) to participants. The latter included infection surveillance[23] and avoidance of neuromuscular blocking agents. If the patient failed to improve LIS (see definition below) between study days 7 and 9, the patient left the treatment arm of the study to receive unblinded methylprednisolone therapy (2 mg/kg/d) for unresolving ARDS following a previously reported protocol (see Web repository for explanation).[9]

Statistical Analysis

The study was analyzed as intention to treat. This study was conducted as a group sequential clinical trial with continuation or

termination determined by periodic inspection as data were accumulated.[24] The primary treatment differences were expected to occur within the first 7 days, and the primary outcome variable was improvement in LIS by study day 7. For patients remaining intubated on study day 7, improvement in lung function was defined as follows: (1) a reduction in LIS $\geq$ 1 point, and (2) a day 7 LIS $\leq$ 2.0 (for study entry LIS $\leq$ 2.9) or $\leq$ 2.5 (for study entry LIS $\geq$ 3.0). At the third analysis (91 patients), there was a significant difference in LIS improvement on day 7 (69.8% vs 35.7%; p = 0.002; power of 0.87). All statistical calculations were preformed using software (SAS System for Windows, Version 9.0; SAS Institute; Cary, NC). Information on statistical analysis is available in the Web-based repository.

Results

Figure 1 shows progress through the phases of the trial. Data are reported as intention to treat for methylprednisolone vs placebo groups. Over the study period, the number of patients recruited each year was as follows: 10, 23, 25, 18, 11, and 4 patients. The baseline characteristics of each group at study entry were similar (Table 1),[25,26] with the exception of a higher proportion of patients with catechol-amine-dependent shock in the control group. In per-protocol analysis (Web repository) the distribution of patients with catecholamine-dependent shock was similar (20% vs 33%; p = 0.21). Extrapulmonary organ dysfunction included cardiovascular (57% vs 68%; p = 0.35), renal (21% vs 25%; p = 0.70), hepatic (13% vs 24%; p = 0.33), and hematologic (16% vs 7%; p = 0.33). Sixty-three patients initially received methylprednisolone, and 28 received placebo. Previously defined criteria for persistent ARDS by Ferguson and collaborators[26] were still present at 24 h in most patients (Table 1).

Changes in LIS and C-reactive protein levels during the first 7 days of the study are shown in Figure 2. By study day 7 (Table 2), the response of the two groups clearly diverged; the methylpred-nisolone-treated group had twice the proportion of patients with a 1-point reduction in LIS (69.8% vs 35.7%; p = 0.002) and breathing without assistance (54.0% vs 25.0%; p = 0.01). Significant differences were also observed for PaO_2/FIO_2 ratio, mechanical ventilation-free days, and MODS score. Single-organ dysfunction by day 7 included pulmonary (40% vs 74%; p = 0.004), cardiovascular (12% vs 37%; p = 0.006), renal (18% vs 37%; p = 0.06), hepatic (9% vs 30%; p = 0.03), and hematologic (13% vs 15%; p = 1.00). Improvement by day 7 correlated with survival by day 7 (R = 0.41; p < 0.001) and hospital survival (R = 0.59; p < 0.001). Mortality by day 7 for patients with catecholamine-dependent shock was similar (80% vs 76.9%). Those with relative adrenal insufficiency had a lower response to methylprednisolone (50% vs 80%; p = 0.05); while among control subjects, adrenal insufficiency also
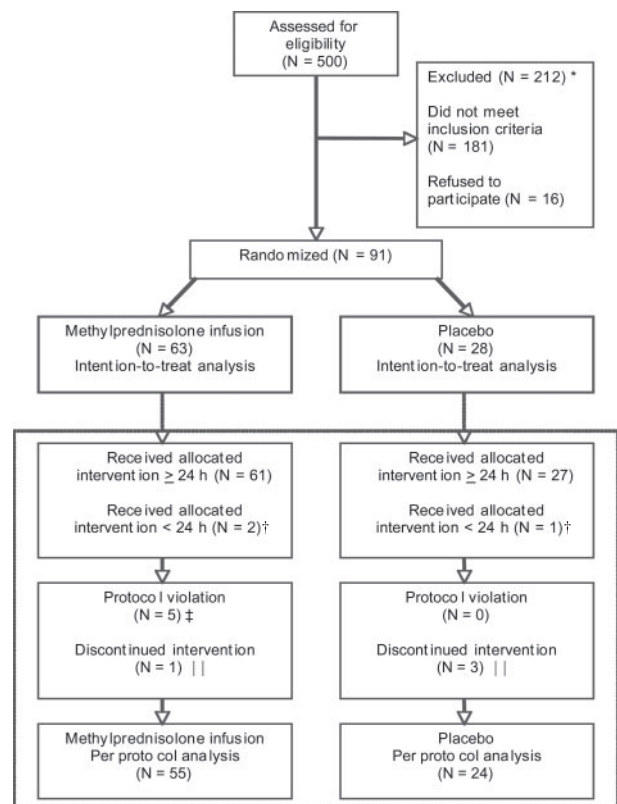

FIGURE 1. Flow diagram of the progress of the trial. *Reasons for exclusion (n = 212): active tuberculosis (n = 3), disease requiring $\geq$ 0.5 mg/kg/d of prednisone equivalent (n = 75), extensive burns (n = 3), HIV positive (n = 10), GI bleeding (n = 18), malignancy with > 50% expected mortality at 6 months (n = 8), moribund or life expectancy < 3 months (n = 12), organ transplant recipients (n = 8), primary physician not committed to full support (n = 34), severe chronic liver disease (n = 22), and other (n = 19). †Received treatment < 24 h (all with catecholamine-dependent shock). Methylprednisolone group: consent withdrawal on the day of study entry (n = 1), and cardiac arrest within 2 h of study entry (n = 1). Placebo group: consent withdrawal (n = 1). ‡Protocol violation (n = 5): after randomization, three patients were recognized to have exclusion criteria: pending HIV test returned positive (n = 1), recently received glucocorticoids (n = 1), and moribund state (n = 1 catecholamine-dependent shock). One patient who required amputation refused aggressive care, and one patient received the study drug adjusted to body weight in pounds instead of kilograms. ‖Discontinued intervention. Methylprednisolone group: one patient had cardiac arrest with anoxic encephalopathy within 24 h of study entry and had supportive care discontinued on study day 6 (catecholamine-dependent shock). Placebo group (n = 3, all with catecholamine-dependent shock): two patients had conditions requiring high-dose glucocorticoids (immune thrombocytopenia and vasculitis), and one patient withdrew consent on study day 3.

affected the proportion of improvement (14% vs 47%; p = 0.19); however, these numbers were too small to detect a statistical difference.

By study day 7, infection surveillance identified 22 nosocomial infections in 19 patients. In methylpred-nisolone-treated patients, 7 of 13 infections (54%) were identified in the absence of fever: 2 ventilator-associated pneumonias, 3 catheter-related infections,

Table 1—*Baseline Patient Characteristics**

Characteristics	Methylprednisolone (n = 63)	Placebo (n = 28)	p Value (n = 91)
Age, yr	50.1 ± 15.3	53.2 ± 15.3	0.38
Male gender	34 (54.0)	13 (46.4)	0.51
White ethnic group†	37 (58.7)	20 (71.4)	0.25
APACHE III score at ICU entry‡	60.2 ± 20.2	57.9 ± 21.0	0.63
Conditions precipitating ARDS§			
Pneumonia	26 (41.3)	12 (42.9)	0.89
Aspiration of gastric content	13 (20.6)	5 (17.9)	0.76
Sepsis (extrapulmonary)	8 (12.7)	7 (25.0)	0.22
Other	16 (25.4)	4 (14.3)	0.24
Direct cause of ARDS	44 (71.0)	16 (59.3)	0.28
Sepsis-induced ARDS	42 (66.7)	19 (67.8)	0.91
Bacteremia	14 (22.2)	6 (21)	0.93
Catecholamine-dependent shock	15 (23.8)	13 (46.4)	0.03
Postsurgical ARDS	22 (34.9)	12 (42.9)	0.47
LIS‖	3.21 ± 0.41	3.11 ± 0.41	0.27
PEEP, cm H_2O	13 ± 5.0	11.2 ± 4.0	0.08
PaO_2/FIO_2 ratio	118.4 ± 51.2	125.9 ± 38.6	0.44
MODS score‖¶	2.1 ± 0.8	2.2 ± 1.1	0.54
C-reactive protein level, mg/dL	25.0 ± 8.8	26.4 ± 10.1	0.55
Baseline cortisol level, μg/dL	21.9 ± 1.8	25.9 ± 1.8	0.21
Adrenal insufficiency‖	16 (25.4)	7 (25.0)	0.88
Persistent ARDS at 24 h#	44 (77.2)	21 (84)	0.49

*Data are presented as mean ± SD or No. (%). At study entry, C-reactive protein levels were available in 80 patients (n = 56 vs 24) and complete APACHE III data were not available in 3 patients (2 receiving methylprednisolone and 1 receiving placebo).

†All but one (Hispanic) of the remaining 34 patients were African American.

‡Scores can range from 0 to 299, with higher scores indicating more severe illness.[25]

§Extrapulmonary sources of sepsis are reported. Methylprednisolone: endocarditis, catheter-related infection, extra-abdominal abscess, pancreatic abscess, urosepsis (n = 2), peritonitis, and other. Placebo: endocarditis, perforated viscous (n = 2), endometritis, necrotizing fasciitis, wound infection, and other. Other conditions precipitating ARDS are reported: methylprednisolone (n = 16); acute pancreatitis (n = 3); multiple blood transfusion (n = 3); postcoronary artery bypass surgery complications (n = 2); near drowning (n = 2); hemorrhagic shock, sickle-cell chest syndrome, abruptio placentae, postpartum complications, and other (n = 2). Placebo: acute myocardial infarction, dissecting aortic aneurysm, mesenteric ischemia, and other. Hospital mortality for conditions precipitating ARDS (methylprednisolone vs placebo): pulmonary infection (n = 5; 21% vs n = 6; 60%), aspiration of gastric contents (n = 2, 18% vs n = 1, 20%), extrapulmonary sepsis (n = 3, 50% vs n = 2; 29%), and other (n = 1; 7% vs n = 0, 0%). Extrapulmonary sepsis associated with hospital death is reported. Methylprednisolone: urosepsis, peritonitis, and endocarditis. Placebo: necrotizing fasciitis and wound infection.

‖See text for definition of LIS and MODS score, and adrenal insufficiency. Additional components for LIS are reported for methylprednisolone vs placebo: static compliance (30.2 ± 8.0 cm H_2O vs 29.6 ± 8.0 cm H_2O; p = 0.74) and chest radiograph score (3.90 ± 0.30 vs 3.89 ± 0.31; p = 0.87). Delivered tidal volume was similar between the two groups (668 ± 157 mL vs 658 ± 141 mL; p = 0.8).

¶If a component MODS value was missing at study entry, the MODS score was imputed when the component value was obtained within 24 h. Unimputed MODS scores were 1.97 ± 0.8 vs 2.14 ± 1.1 (p = 0.46).

#Persistent ARDS criteria at 24 h was defined as a PaO_2/FIO_2 ratio ≤ 200 on PEEP and standardized ventilatory management.[26] Includes 82 patients (n = 57 vs 25) with available arterial blood gas values on day 1.

1 urinary tract infection, and 1 wound infection. Treated patients had a trend toward decreased incidence of ventilator-associated pneumonia (p = 0.06).

Between day 7 and day 9, 14 patients failed to meet predefined criteria for improvement in LIS (8% vs 36%; p = 0.002) and received open-label methylprednisolone (2 mg/kg/d) for unresolving ARDS.[9] Of the 15 control patients receiving mechanical ventilation on day 9, 5 patients met criteria for improvement in LIS, and 10 nonimprovers received open label methylprednisolone (2 mg/kg/d) for unresolving ARDS.

As shown in Table 3, the treatment group had a significant reduction in duration of mechanical ventilation, length of ICU stay, and ICU mortality; a trend toward significant reduction in hospital mortality (p = 0.07) was observed. ICU mortality for patients with catecholamine-dependent shock was 73% vs 46% (p = 0.24), and for patients without shock was 81% vs 67% (p = 0.29). In per-protocol analysis (Web repository), ICU mortality for patients with catecholamine-dependent shock was 90% vs 71% (p = 0.07). Among survivors, the treatment group had a significant reduction in duration of mechanical ventilation (median, 5.5 days [range, 4 to 8.5 days] vs 9.5 days [range, 6 to 20 days]; p = 0.004), ICU stay (median, 7.5 days [range, 6 to
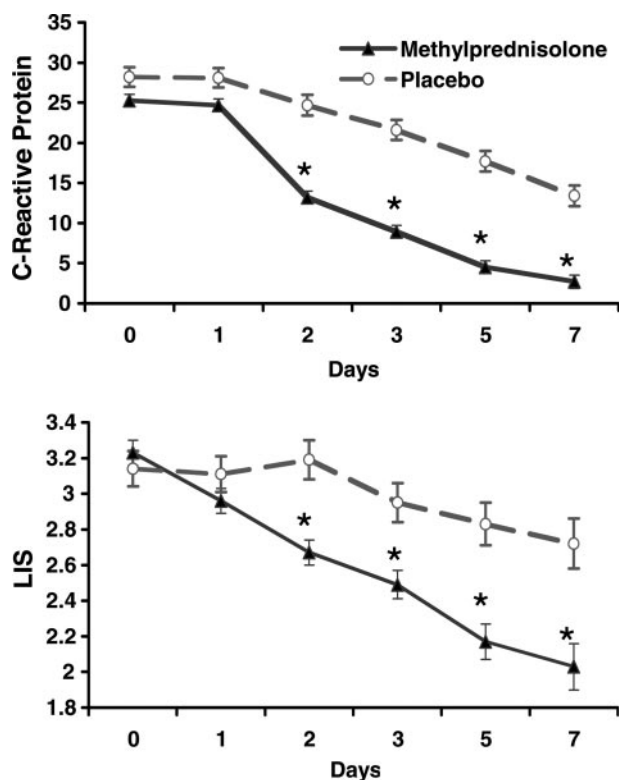
FIGURE 2. Changes in C-reactive protein and LIS over 7 days for patients randomized to methylprednisolone (n = 63) and placebo (n = 28). *p < 0.001.

12 days] vs median, 16 days [range, 9.5 to 25.5 days]; p = 0.001), and hospital stay (median, 14 days [range, 10 to 20 days] vs median, 30 days [range, 13.5 to 61.5 days]; p = 0.005). Figures 3, 4 show Kaplan-Meier probability estimates for continuation of mechanical ventilation and survival curves, respectively. After study day 14, 3 patients (5%) in the treatment group and 10 patients (36%) in the control group remained on mechanical ventilation (p < 0.0001). Mortality rates at 2, 6, and 12 months were 76% vs 61% (p = 0.13), 67% vs 46% (p = 0.07), and 63.5% vs 46% (p = 0.13), respectively.

Complications and infections observed during treatment are shown in Table 4. One hundred thirty-five bronchoscopies with BAL were performed during the study: 83 at study entry, 21 during the first week, and 31 after day 7. The treated patients had a significantly (p = 0.0002) lower rate of infections. In the treatment group, among the 27 infections developing after day 7, 16 infections (60%) were identified in the absence of fever: 3 ventilator-associated pneumonias, 3 catheter-related infections, 4 urinary tract infection, 2 intra-abdominal infections, 2 primary bacteremia, 1 sinusitis, and 1 other. Three of the five patients with neuromuscular weakness (Table 4) were receiving mechanical ventilation

for > 10 days; the control patients received open-label methylprednisolone for unresolving ARDS. One of five patients with neuromuscular weakness, randomized to methylprednisolone, was a nonsurvivor.

DISCUSSION

This is the first randomized controlled trial investigating the efficacy and safety of low-dose prolonged methylprednisolone administration in early ARDS. This study tested a pathophysiologic model that placed dysregulated systemic inflammation at the pathogenetic core of ARDS,[1] and evaluated the effect of prolonged low-dose glucocorticoid treatment on biological and physiologic responses related to inflammation. The surrogate marker for pulmonary inflammation was LIS; the markers for systemic inflammation were C-reactive protein and MODS. The findings of this study support our original hypothesis that down-regulation of systemic inflammation with early introduction of prolonged glucocorticoid treatment hastens resolution of pulmonary organ dysfunction in ARDS. The findings in the intention-to-treat and per-protocol analysis (Web repository) were similar.

By study day 7, the response to prolonged methylprednisolone infusion at a dosage of 1 mg/kg/d was remarkable, with twice the proportion of patients randomized to methylprednisolone achieving the primary end point of a 1-point reduction in LIS and breathing without assistance. Treated patients had a significant reduction in C-reactive protein levels and by study day 7 had, in comparison to control patients, significantly lower LIS and MODS score and more ventilator-free days. After day 7, comparison between the two groups was skewed by the fact that 10 of the 15 control patients (67%) remaining on mechanical ventilation received open-label methylprednisolone (2 mg/kg/d) for unresolving ARDS. Patients randomized to methylprednisolone treatment had a significant reduction in duration of mechanical ventilation and ICU length of stay. Improvement on day 7 was not significantly affected by the baseline imbalance in the proportion of patients with catecholamine-dependent shock, and correlated with ICU and hospital survival. The survival difference observed during hospitalization was preserved after 1 year.

Innate or treatment-induced down-regulation of systemic inflammation is important to the resolution of sepsis and ARDS.[1] All randomized trials of sepsis[11,17,27–29] and ARDS[8,12,13,19] with positive findings reported a significant reduction in circulating levels of inflammatory cytokines and/or C-reactive protein

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Table 2—Outcome Measures on Study Day 7*

Variables	Methylprednisolone (n = 63)	Placebo (n = 28)	Relative Risk (95% Confidence Interval) [n = 91]	p Value
Extubated or with $\geq$ 1-point reduction in LIS	44 (69.8)	10 (35.7)	1.96 (1.16–3.30)	0.002
Patients breathing without assistance	34 (54.0)	7 (25.0)	2.16 (1.09–4.26)	0.01
LIS† (mean $\pm$ SE)	2.14 $\pm$ 0.12	2.68 $\pm$ 0.14		0.004
PaO_2/FIO_2 ratio in ventilated patients (mean $\pm$ SE)	256 $\pm$ 19	179 $\pm$ 21		0.006
PEEP, cm H_2O	10.1 $\pm$ 4.6	12.9 $\pm$ 5.3		0.10
Mechanical ventilation-free days‡	2.2 $\pm$ 2.1	1.1 $\pm$ 1.9		0.02
MODS score†§	0.90 $\pm$ 1.1	1.9 $\pm$ 1.4		0.002
Patients with MODS score > 1	33 (54.1)	23 (85.2)	0.64 (0.48–0.84)	0.005
C-reactive protein level, mg/dL	2.9 $\pm$ 4.1	13.1 $\pm$ 6.8		< 0.0001
Cortisol level, μg/dL	5.7 $\pm$ 2.1	18.0 $\pm$ 1.6		< 0.0001
Patients with new infection‖	10 (15.9)	8 (28.6)	0.56 (0.25–1.26)	0.16
Patients with ventilator-associated pneumonia	4 (6.4)	6 (21.4)	0.30 (0.09–0.97)	0.06
Survivors	56 (88.9)	22 (78.6)	1.13 (0.92–1.40)	0.21
Patients with unresolving ARDS treated with open-label methylprednisolone at 2 mg/kg/d¶	5 (7.9)	10 (35.7)	0.22 (0.08–0.59)	0.002

*Data are presented as mean $\pm$ SD, No. (%) unless otherwise indicated.

†LIS, PaO_2/FIO_2 ratio, and PEEP values from patients receiving mechanical ventilation on study day 7. Additional components for LIS are reported for methylprednisolone vs placebo: static compliance (33.9 $\pm$ 11.5 cm H_2O vs 31.9 $\pm$ 17.7 cm H_2O; p = 0.69) and chest radiograph score (3.0 $\pm$ 1.3 vs 3.4 $\pm$ 1.1; p = 0.26). The number of ventilator-free days was defined as the number of days on which a patient breathed without assistance, if the period of unassisted breathing lasted at least 48 consecutive h. The number was counted as 0 if the patient died before day 28.

‡If MODS value was missing on study day 7, the MODS score was imputed using the last available component value. The unimputed MODS scores were 0.6 $\pm$ 0.8 vs 1.3 $\pm$ 0.9 (p = 0.007).

§Three treated patients and one control patient had two infections. Extrapulmonary infections (methylprednisolone vs placebo) included urinary tract infections (n = 3 vs 1), catheter-related infections (n = 4 vs 0), intra-abdominal abscess (n = 0 vs 1), primary bacteremia (n = 0 vs 1), sinusitis (n = 1 vs 0), and wound infection (n = 1 vs 0).

‖If the LIS failed to improve LIS (see text for definition) between study days 7 and 9, the patient left the treatment arm of the study to receive unblinded methylprednisolone therapy (2 mg/kg/d) for unresolving ARDS following a previously reported protocol.[9]

over time. Glucocorticoids as end-effectors of the hypothalamic-pituitary-adrenal axis are the most important physiologic inhibitors of inflammation,[30] affecting hundreds of genes involved in stress-related homeostasis.[31] At the cellular level, glucocorticoids exert their effects by activating cytoplasmic heat shock protein-complexed glucocorticoid receptors, which in turn interact with activated nuclear factor-κB to prevent DNA binding and subsequent transcriptional activity.[30] Using an *ex vivo* model of systemic inflammation, we reported that naïve peripheral blood leukocytes exposed to longitudinal plasma samples collected during prolonged methylprednisolone treatment of unresolving ARDS exhibited a progressive increase in cytoplasmic binding of glucocorticoid receptor to nuclear factor-κB, and a concomitant reduction in nuclear factor-κB DNA binding and transcription of tumor necrosis factor-α

Table 3—Duration of Mechanical Ventilation and Length of Stay; ICU and Hospital Mortality*

Variables	Methylprednisolone (n = 63)	Placebo (n = 28)	Relative Risk (95% Confidence Interval) [n = 91]	p Value
Duration of mechanical ventilation, d†	5 (3–8)	9.5 (6–19.5)		0.002
Mechanical ventilation-free days to day 28‡	16.5 $\pm$ 10.1	8.7 $\pm$ 10.2		0.001
Length of ICU stay, d	7 (6–12)	14.5 (7–20.5)		0.007
Survivors of ICU admission	50 (79.4)	16 (57.4)	1.39 (0.98–1.96)	0.03
Length of hospital stay	13.0 (8–21)	20.5 (10.5–40.5)		0.09
Survivors of hospital admission	48 (76.2)	16 (57.1)	1.33 (0.94–1.89)	0.07

*Data are presented as mean $\pm$ SD, No. (%), and median (interquartile range) unless otherwise indicated.

†The proportion of patients remaining on mechanical ventilation on study day 14 and day 28 (methylprednisolone vs placebo) was 4 (6.4%) vs 12 (42.9%) [p < 0.001] and 3 (4.7%) vs 4 (14.2%) [p = 0.20], respectively.

‡The number of ventilator-free days was defined as the number of days a patient breathed without assistance, if the period of unassisted breathing lasted at least 48 consecutive h. The number was counted as 0 if the patient died before day 28.
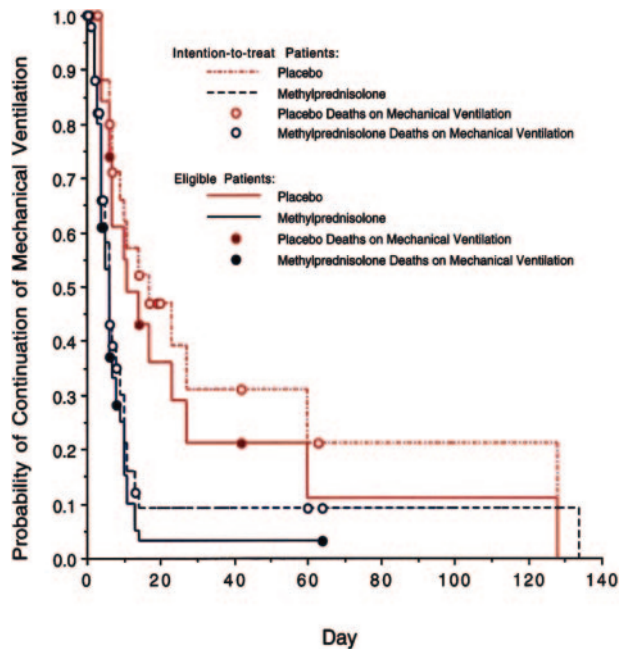
FIGURE 3. Kaplan-Meier probability estimates for continuation of mechanical ventilation for patients randomized to methylprednisolone and placebo for intention-to-treat and eligible patients. Kaplan-Meier log-rank p values for the intention-to-treat and fully eligible curves are 0.001 and < 0.001, respectively. Blue lines and red lines represent methylprednisolone and placebo, respectively. Dashed lines and solid lines represent intention-to-treat (n = 91) and eligible patients (n = 72), respectively. Solid and open circles represent censoring of mechanical ventilation duration for deaths occurring on mechanical ventilation.

FIGURE 4. Survival curves for patients randomized to methylprednisolone and placebo for intention-to-treat (n = 91) and eligible (n = 72) patients. Kaplan-Meier log-rank p values for the intention-to-treat and fully eligible curves are 0.06 and 0.13, respectively. Blue lines and red lines represent methylprednisolone and placebo, respectively. Survival data up to 1 year with intention-to-treat analysis (dashed lines) of 91 patients randomized to methylprednisolone (n = 63) vs placebo (n = 28): 7 days, 88.9% vs 78.6% (p = 0.20); 28 days, 81% vs 64.3% (p = 0.09); 60 days, 76.2% vs 60.7% (p = 0.13); 6 months, 66.7% vs 46.4% (p = 0.07); and 1 year, 63.5% vs 46.4% (p = 0.13). Survival data up to 1 year for the 72 fully eligible patients (solid lines) randomized to methylprednisolone (n = 51) vs placebo (n = 21): 7 days, 96.1% vs 81% (p = 0.06); 28 days, 88.2% vs 76.4% (p = 0.20); 60 days, 86.3% vs 71.4% (p = 0.14); 6 months, 74.5% vs 57.1% (p = 0.15); and 1 year, 70.6% vs 57.1% (p = 0.27).

and interleukin-1β.[8] These findings provided mechanistic evidence of the pharmacologic efficacy of methylprednisolone in ARDS.

Dosage and duration of administration are fundamental variables that considerably affect the response to a pharmacologic intervention and must be taken into account in designing a trial and in analyzing the literature.[32] Our study design differs from an older trial[6] with negative findings that investigated a daily methylprednisolone dose of 120 mg/kg and limited duration of administration to 24 h. In sepsis trials, a linear relation has been reported[33] between dose and/or duration and survival (p = 0.02), with increased survival at lower doses with prolonged treatment, but increased mortality at higher doses with brief treatment. Moreover, methylprednisolone at high dose (15 to 30 mg/kg/d), but not low dose, is associated with measurable immunosuppression.[28,34]

In ARDS, the circulating half-life of methylprednisolone (1 mg/kg) varies from 3.8 to 7.2 h, with greatly diminished effects (irrespective of dosage) expected after 24 to 36 h.[28,34,35] Experimental and clinical literature support the concept that duration of exposure to glucocorticoids is critical to achieving regulati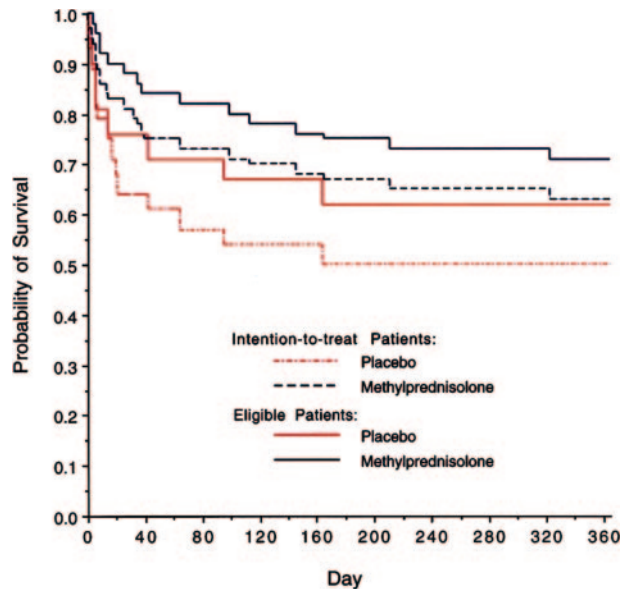on of cytokine production and demonstrable therapeutic benefits.[28,36] In experimental models of acute lung injury, glucocorticoid administration was shown to be effective in decreasing edema and lung collagen formation with prolonged treatment, while premature withdrawal rapidly negated the positive effects of therapy.[37–39] In patients with unresolving ARDS, premature discontinuation of methylprednisolone administration was associated with physiologic deterioration[10,13,40,41] that responded favorably to reinstitution of treatment.[40,41] In the recent ARDS network study,[13] the large benefits observed during methylprednisolone treatment of unresolving ARDS (27% relative risk reduction in mortality; 10 days reduction in duration of mechanical ventilation [p = 0.006]) were partially lost after premature discontinuation of study drug (within 4 days of extubation) and likely accounted for the higher rate of reintubation (9% vs 28%; p = 0.006).

Since the 1950s, it has been appreciated that a serious threat to the recovery of patients receiving prolonged glucocorticoid treatment is failure to recognize infections in the presence of a blunted febrile

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Table 4—Complications Observed During the Study*

Variables	Methylprednisolone (n = 63)	Placebo (n = 28)	Relative Risk (95% Confidence Interval) [n = 91]	p Value
Patients with new infection after study entry, No. (%)	27 (42.9)	17 (60.7)	0.49 (0.20–1.20)	0.17
Total new infections, No.†	40	40		0.0002
Pneumonia	9	16		0.004
Sinusitis	3	0		
Catheter-related infection	8	5		0.56
Urinary tract infection	8	8		0.10
Intra-abdominal infection‡	3	4		0.13
Bacteremia (primary)	5	5		0.19
Candidemia§	2	1		0.93
Others‖	2	1		0.93
Pneumothorax¶	5 (7.9)	6 (21.4)	0.37 (0.12–1.11)	0.09
Neuromuscular weakness#	4 (6.4)	1 (3.6)	1.78 (0.21–15.20)	1.0
Hyperglycemia requiring insulin	45 (71.4)	18 (64.3)	1.11 (0.81–1.53)	0.50
Other complications**	3 (4.8)	0 (0)	3.17 (0.17–59.43)	0.55

*Data are presented as No. (%) or No. unless otherwise indicated. Values are reported for eligible patients.

†Assessed by the goodness-of-fit χ^2 test. Given 80 total infections, the observed number of infections (40 vs 40) is compared to the expected numbers (52.2 vs 24.8) given proportions of patients in each treatment group. There were fewer-than-expected observed infections in the methylprednisolone group. Specific infections are expressed in terms of observed infections per total number of infections in each treatment group. Six of the 80 identified infections did not meet preestablished definitive criteria (see text for explanation): ventilator-associated pneumonia (n = 1), sinusitis (n = 2), and urinary tract infection (n = 3); all occurred in patients randomized to methylprednisolone. Number of infections developing at different time intervals in patients randomized to methylprednisolone: day 2 to 7, n = 13; day 7 to 14, n = 12; day 14 to 21, n = 7; day 21 to 28, n = 7; after day 28, n = 3. Among the 15 placebo-treated patients receiving mechanical ventilation after day 7, infections developed in the 3 of the 5 patients who did not require and in 8 of 10 patients who did require open-label methylprednisolone for unresolving ARDS. In the former group, the three patients had five infections: one ventilator-associated pneumonia, one catheter-related infection, two urinary tract infections, and one intra-abdominal infection. In the latter group, two patients had an infection within 24 h of receiving open-label methylprednisolone (bacteremia and catheter-related infection); six patients had 15 infections during open-label methylprednisolone treatment (ventilator-associated pneumonia, n = 8; catheter-related infection, n = 2; bacteremia, n = 2; candidemia, n = 1; urinary tract infection, n = 1; and extra-abdominal abscess, n = 1), and three patients had 9 infections after termination (from study day 42 to 78) of methylprednisolone (ventilator-associated pneumonia, n = 1; catheter-related infection, n = 2; bacteremia, n = 1; urinary tract infection, n = 3; and intra-abdominal infection, n = 2).

‡Intra-abdominal infections developed in two patients in each group; three of the four patients had two separate episodes at least 10 days apart. Timing of infection for patients randomized to methylprednisolone treatment was study days 16 and 27 in one patient, and day 21 in the other. Timing of infection for patients randomized to placebo treatment was days 6 and 16 in one patient who did not require open-label methylprednisolone, and days 42 and 54 for a patient who received 32 days of open-label methylprednisolone starting on study day 7.

§Candidemia was detected in one patient in each group. One patient randomized to methylprednisolone had two episodes on study days 20 and 27. One patient randomized to placebo had one episode on study day 15, 8 days after initiation of open-label methylprednisolone for unresolving ARDS.

‖Methylprednisolone: wound infection, and endocarditis; placebo: extra-abdominal abscess.

¶Mean duration of mechanical ventilation (days) in patients with and without pneumothorax was 29.7 + 25.7 days vs 7.8 + 3.7 days (p = 0.09).

#Three of the five patients with neuromuscular weakness were receiving mechanical ventilation for > 10 days (27 days, 64 days, and 134 days), and one patient was a nonsurvivor (randomized to methylprednisolone). The only control patient failed to improve LIS and received open-label methylprednisolone for unresolving ARDS.

**Pancreatitis, n = 2; GI bleeding requiring transfusion, n = 1.

response.[42,43] In our prior study,[9] four of nine pneumonia cases were identified by surveillance bronchoscopy in treated patients without fever. In the present study, 23 of 40 nosocomial infections (56%) including 5 of 10 ventilator-associated pneumonia cases were identified by infection surveillance in treated patients without fever. These findings underscore the need for strict infection surveillance in the management of patients receiving prolonged glucocorticoid treatment.[32] Among the 73 patients (including 10 control nonimprovers) who received methylprednisolone, 3 patients (4%) had prolonged neuromuscular weakness and delayed weaning. The percentage incidence is lower than that reported in the ARDSnet study[13] and is likely related to the lower dose of methylprednisolone and the limited use of neuromuscular blocking agents.

Many of the positive results of this trial are similar to those reported in randomized studies investigating prolonged glucocorticoid treatment in acute lung injury and ARDS. Improvement in gas exchange and reduction in duration of mechanical ventilation were previously reported for patients with early acute lung injury,[11] septic shock-induced ARDS,[12] and unresolving ARDS.[9,13] Both trials[10,13] in unresolving ARDS showed that earlier introduction of prolonged

methylprednisolone treatment was associated with a higher rate of clinical improvement. In the ARDS network trial,[29] however, large imbalances in baseline characteristics for patients randomized after day 14 (age, gender, pneumonia, trauma, creatinine, APACHE (acute physiology and chronic health evaluation) III, compliance, and lung injury score) likely affected the lower mortality in the control group (8% vs 36%). In a study by Lee et al,[44] prolonged methylprednisolone (2 mg/kg/d) treatment in patients with early ARDS following thoracic surgery was associated with, in comparison to historical control subjects, a significant reduction in duration of mechanical ventilation, ICU stay, and hospital mortality.

The reduction in C-reactive protein observed during treatment is comparable to the reduction reported for patients with community-acquired pneumonia and acute lung injury,[11] and is similar to the reduction in systemic inflammation shown in other randomized studies.[9,12,13] Resolution of cardiac dysfunction is consistent with the beneficial effect of prolonged glucocorticoid treatment on shock reversal in septic patients.[33] In agreement with reports on sepsis[33] and unresolving ARDS,[8,13] prolonged glucocorticoid treatment was not associated with increased risk of infections, and our data add clinical relevance to the new understanding of the immunoenhancing role of low-dose glucocorticoids.[28,45]

Study limitations are attributed primarily to the small sample size and imbalances among patients with catecholamine-dependent shock that may have biased the estimate of the treatment effect on mortality, and a larger randomized trial is necessary to support the mortality findings of this study. Additional limitations include previously reported limitations in chest radiograph scoring in patients with ARDS,[46] failure to incorporate a weaning procedure, and failure to strictly monitor implementation of ventilator protocol.

In conclusion, the findings of this study provide evidence that glucocorticoid treatment-induced down-regulation of systemic inflammation in ARDS is associated with a significant improvement in pulmonary and extrapulmonary organ dysfunction and a reduction in duration of mechanical ventilation and ICU length of stay. The approximate cost of 28 days of therapy was $240. A larger trial is necessary to confirm the mortality findings of this study. In a future trial, we recommend adding stratification by shock at study entry, and strict implementation and monitoring of a ventilator and weaning protocol.

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