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SYSTEMATIC REVIEW

G. Umberto Meduri
Lisa Bridges
Mei-Chiung Shih
Paul E. Marik
Reed A. C. Siemieniuk
Mehmet Kocak

Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature

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G. U. Meduri (✉) · L. Bridges
Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Memphis Veterans Affairs Medical Center (111), 1030 Jefferson Avenue, Suite Room #CW444, Memphis, TN 38104, USA
e-mail: gmeduri@uthsc.edu
Tel.: +1-901-5777520

M.-C. Shih
Department of Veterans Affairs, Cooperative Studies Program Coordinating Center, Palo Alto, CA, USA

M.-C. Shih
Department of Health Research and Policy, Stanford University, Stanford, CA, USA

P. E. Marik
Division of Pulmonary and Critical Care Medicine, Department of Medicine, Eastern Virginia Medical School, Norfolk, VA, USA

R. A. C. Siemieniuk
Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada

R. A. C. Siemieniuk
Department of Medicine, University of Toronto, Toronto, ON, Canada

M. Kocak
Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

Abstract *Purpose:* To investigate the effect of prolonged glucocorticoid treatment for patients with acute respiratory distress syndrome (ARDS). *Methods:* We conducted two sets of intention-to-treat analyses: (1) a primary analysis of individual patients' data (IPD) of four randomized controlled trials (RCTs) which investigated methylprednisolone treatment ($n = 322$) and (2) a trial-level meta-analysis incorporating four additional RCTs which investigated hydrocortisone treatment in early ARDS ($n = 297$). We standardized definitions to derive outcomes in all datasets. The primary outcome for the IPD analysis was time to achieving unassisted breathing (UAB) by study day 28. Secondary outcomes included mechanical ventilation (MV) and intensive care unit (ICU)-free days, hospital mortality, and time to hospital mortality by day 28. *Results:* By study day 28, compared to the placebo group, the methylprednisolone group had fewer patients who died before achieving UAB (12 vs. 29 %; $p < 0.001$) and more patients who achieved UAB (80 vs. 50 %; $p < 0.001$). In the methylprednisolone group, time to achieving UAB was shorter [hazard ratio 2.59, 95 % confidence interval (CI) 1.95–3.43; $p < 0.001$], and hospital mortality was decreased (20 vs. 33 %; $p = 0.006$), leading to increased MV (13.3 ± 11.8 vs. 7.6 ± 5.7; $p < 0.001$) and ICU-free days (10.8 ± 0.71 vs. 6.4 ± 0.85; $p < 0.001$). In those patients randomized before day 14 of ARDS onset, the trial-level meta-analysis indicated decreased hospital mortality (36 vs. 49 %; risk ratio 0.76, 95 % CI 0.59–0.98, $I^2 = 17$ %, $p = 0.035$; moderate certainty). Treatment was not associated with increased risk for infections (risk ratio 0.77, 95 % CI 0.56–1.08, $I^2 = 26$ %; $p = 0.13$; moderate certainty). *Conclusions:* Prolonged methylprednisolone treatment accelerates the resolution of ARDS, improving a broad spectrum of interrelated clinical outcomes and decreasing hospital mortality and healthcare utilization.

Keywords Adult respiratory distress syndrome · Glucocorticoid treatment · Mechanical ventilation · Survival

Introduction

Acute respiratory distress syndrome (ARDS) is a disease of multifactorial etiology characterized by severe and diffuse inflammatory exudate of the pulmonary lobules, leading to hypoxemic respiratory failure requiring mechanical ventilation (MV) [1, 2]. Translational research has established a strong association between dysregulated systemic inflammation and progression (maladaptive repair) or delayed resolution of ARDS [1, 3]. In patients with ARDS, glucocorticoid receptor-mediated downregulation of systemic and pulmonary inflammation is essential to restore tissue homeostasis and accelerate disease resolution, and it can be significantly enhanced with prolonged low-to-moderate dose glucocorticoid treatment [1].

A consistent body of evidence supports a strong association between prolonged glucocorticoid treatment-induced downregulation (resolution) of the inflammatory response and improvement in pulmonary (adaptive lung repair) and extra-pulmonary physiology [Electronic Supplementary Material (ESM)] [1]. Evidence from meta-analyses of randomized controlled trials (RCTs) in support of prolonged glucocorticoid treatment is, however, inconsistent due to: (1) the lack of a large RCT, (2) the failure to account for important inter-RCT differences in the design of the treatment protocol, and (3) the inclusion in meta-analyses of older RCTs which investigated a time-limited (24–48 h) massive daily methylprednisolone dose (up to 120 mg/kg/day) [4].

Lacking a large confirmatory trial, analysis of individual patient data (IPD) from small to moderately sized trials can provide an improved measure of treatment effectiveness [5]. We conducted an IPD analysis of four RCTs [6–9] which investigated methylprednisolone treatment ($n = 322$). We hypothesized that prolonged methylprednisolone treatment, in comparison to placebo, would accelerate disease resolution, leading to a shorter duration of assisted breathing (primary outcome). Secondary outcomes were MV-free days, intensive care unit (ICU)-free days, and time to hospital mortality, and hospital mortality by day 28.

Fundamental variables of a treatment protocol that may significantly affect overall response to glucocorticoid treatment include timing of treatment initiation, dosage, duration of administration, and tapering [1]. Since the RCTs included here for analysis differ in timing of treatment initiation (early [6, 7] vs. late [8, 9]) and speed of drug tapering (slow [6–8] vs. rapid [9]) after achieving unassisted breathing (UAB), the IPD analysis also provides a unique opportunity to study the impact of these treatment characteristics on outcomes. We hypothesized that timing to achieving UAB would be shorter with early initiation of treatment and that rapid tapering of methylprednisolone treatment after removal of initial AB would increase the risk for recrudescence of ARDS (caused by rebound inflammation in the presence of impaired adrenal response) and return to AB [10].

Finally, the findings of the IPD analysis were incorporated into a trial-level meta-analysis of the available literature—limited to RCTs investigating prolonged (≥7 days) treatment—that included an additional four RCTs [11–14] which had investigated hydrocortisone treatment in early ARDS ($n = 297$).

Methods

The first set of analyses was an IPD analysis from all four RCTs investigating prolonged methylprednisolone treatment initiated in early (<72 h; $n = 118$) [6, 7] and late (after 5–7 days; $n = 204$) [8, 9] ARDS. ARDS was defined according to the Berlin consensus definition [3]. These four RCTs [6–9] included improvement in lung function and/or duration of MV as a primary [6–8] or secondary [9] end-point (ESM Table S1). We received institutional review board (IRB no: 382094-3) approval for access to the datasets for three trials [6, 8, 9] and to some components of the Rezk et al. dataset [7]. Before the IPD analysis we standardized definitions to derive outcomes in all datasets [6–9].

The primary outcome of the IPD analysis was time to successful removal of initial AB (followed by 48 h of UAB) by study day 28. In this study, AB refers to invasive MV. This outcome reflects resolution of the acute phase (respiratory failure) of ARDS [1] and—based on the trials' designs [6–9]—most patients received the study drug until they achieved UAB by day 28. Secondary outcomes included MV-free days, ICU-free days, hospital mortality, time to death by hospital discharge or by day 28 (particularly for those randomized before day 14 of ARDS [10]), and infectious complications. Return to AB or the ICU were included in the calculation of total duration of MV or ICU stay to study day 28. More detailed descriptions of the definitions of the outcomes are given in the ESM. Pre-specified subgroup analyses included: (1) timing of treatment initiation [early (≤day 3) [6, 7] vs. late (≥day 5) [8, 9], and <day 14 vs. day 14–28]; (2) speed of tapering of study treatment after achieving initial UAB (slow [6–8] vs. rapid [9]); (3) baseline characteristics {age, gender, and Sequential Organ Failure Assessment (SOFA) score [15]}.

Data on duration of treatment were available in three methylprednisolone trials [6, 8, 9] and derived from the values reported in the publication of the fourth trial [7]. Duration of initial AB not limited to day 28 was provided as an aggregate in the publication by the ARDS network [9] and derived from IPD in the other trials [6–8]. The following outcomes were available for the first 28 days

for all four studies: (1) duration of study treatment; (2) duration of initial AB (followed by 48 h of UAB); (3) return to AB (in one trial [9], study day of return to AB was not available) and additional days on AB until day 28; (4) duration of ICU stay, re-admission to ICU, and additional ICU days until day 28; (5) length of hospital stay. Reasons for return to AB and to the ICU were not available in one trial [9]. Data on survival to day 28 (irrespective of location) and on hospital discharge were available in all trials, and data on survival after hospital discharge were available in two trials [6, 8] and provided until day 180 only for those not discharged home ($n = 49$) in one trial [9]. Age, gender, and data for measurement of the SOFA score [15] were available for three trials [6, 8, 9].

Our updated trial-level meta-analysis incorporated four additional RCTs which had investigated 7 days of hydrocortisone treatment in early ARDS [11–14]. The literature search methodology and details on these hydrocortisone RCTs are provided in the ESM. Two reviewers independently assessed risk of bias with a modified Cochrane tool [16], and disagreements were resolved by consensus. We assessed certainty in evidence for each outcome using the GRADE system [17], and for each outcome, we present the more credible effect estimate of either the IPD or trial-level meta-analysis. Where certainty in evidence was judged to be the same for both estimates, we chose to use the more conservative point estimate.

Statistical analysis

The IPD analyses were performed according to the intention-to-treat principle. Continuous variables were summarized by means and standard errors and compared between the two treatment groups by using multiple linear regressions, adjusting for study. Binary data were summarized by frequencies and percentages and compared between the treatment groups using logistic regression models, adjusting for study. For within-study comparisons of the treatment groups, we used Wilcoxon–Mann–Whitney tests for continuous variables and chi-square tests for binary variables.

Cumulative incidence curves and competing risk analyses stratified by study [18] were used to compare time to UAB between the treatment groups; Kaplan–Meier curves and stratified log-rank tests were used to compare time to death up to initial hospital discharge or day 28. The estimated hazard ratios (HRs), 95 % confidence intervals (CI), and p values were provided. Competing risks regression analyses [19] and proportional hazards regression (Cox regression) models were constructed for time to UAB and time to death by day 28, respectively, to assess the treatment effect, with adjustment for selected covariates, including individual study characteristics (treatment initiation and speed of tapering) and patient characteristics [such as age categories ($\leq$55 vs. >55 years), gender, SOFA categories ($\leq$7 vs >7)] and to assess potential interactions between treatment and these covariates. The proportionality assumptions were tested using the Schoenfeld residuals method [20]. The dichotomized version of age and SOFA score was constructed using a locally weighted scatterplot smoother (LOESS smoother) of the Martingale residuals [20]. IPD on patients' characteristics were not available in the study by Rezk et al. [7], and thus this study was excluded from the regression models whenever these covariates were needed. Since some of the covariates of interest are study characteristics, such as treatment initiation and speed of tapering, we were not able to adjust for study in the regression models to account for other potential differences between individual studies. All analyses were repeated in the subgroup of patients randomized before day 14 of ARDS since there is a broad consensus that glucocorticoid treatment should be initiated before day 14 of ARDS. We did not analyze the subgroup randomized after day 13 of ARDS nor did we formally test whether the methylprednisolone effect differed between these two subgroups.

All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC). A two-sided p value of <0.05 was considered to indicate statistical significance, except for the tests conducted on secondary outcomes, where a lower significance level of 0.001 was used based on the Bonferroni multiplicity correction approach.

We performed a trial-level meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [21] of randomized clinical trials conducted in adults with ARDS comparing treatment with glucocorticoids to placebo. Prespecified outcomes were MV-free days, ICU-free days, in-hospital mortality, and development of nosocomial infections. A priori we were interested in hospital mortality for the subgroup of patients randomized before day 14 of ARDS onset. We used a random-effects model with DerSimonian–Laird 95 % CIs. Categorical variables were summarized with relative risk (RR) and continuous variables with mean difference. Meta-analysis was performed using Review Manager version 5.2 (The Cochrane Collaboration, Copenhagen, Denmark).

We assessed heterogeneity between studies for each outcome using I^2, with suggested thresholds for low (25–49 %), moderate (50–74 %) and high (>75 %) values. Subgroup analyses were performed for type of glucocorticoid used, year of publication (before 2010 vs. after 2010), each risk of bias category, and size of study (<60 patients vs. $\geq$60 patients). We performed sensitivity

analyses excluding RCTs with the sequential stopping rule.

Results

Analysis of IPD from RCTs investigating prolonged methylprednisolone treatment ($n = 322$)

In the two early [6, 7] and two late ARDS trials [8, 9], the initial daily methylprednisolone dosage was 1 and 2 mg/kg/day and the duration of treatment extended up to 25 and 32 days, respectively. The ARDS network trial [9], in comparison to the other trials [6–8], had a significantly ($p < 0.001$) shorter duration of treatment (ESM Table S2; Fig. S1). Shorter duration of treatment [9] was accounted for by two factors: (1) removal of study drug before completion of study protocol and achieving initial UAB ($n = 31$) and (2) rapid tapering after achieving initial UAB (3.1 ± 1.1 days). More details are provided in the ESM.

The design of each study [6–9] and participants' baseline characteristics (ESM Table S1) suggest that there were no significant differences in age, gender, SOFA score, ideal body weight-adjusted tidal volume, and PEEP requirements. In all of these four trials [6–9], methylprednisolone administration was associated with a significant downregulation of systemic inflammation (reduction in inflammatory cytokines [6, 8, 9] and/or C-reactive protein levels [6–8]). The effects of prolonged methylprednisolone treatment on primary and secondary outcomes are shown in Fig. 2 and Table 1 as an aggregate and in ESM Table S3 for each trial individually. The GRADE summary findings for all RCTs (methylprednisolone [6–9] and hydrocortisone [11–14]) are shown in Table 2. Unless specified otherwise, comparison between groups is reported as methylprednisolone versus placebo.

By study day 28, compared to the placebo group the methylprednisolone group had fewer patients who died before achieving UAB (12 vs. 29 %), more patients who achieved UAB (80 vs. 50 %), fewer patients alive on day 28 who had remained on initial AB (8 vs. 21 %; Fig. 1), and more patients discharged alive from the ICU (75 vs. 49 %); all p values <0.001. By day 28, those in the methylprednisolone group had achieved initial UAB earlier (12.4 ± 0.61 vs. 19.8 ± 0.78 days; HR 2.59, 95 % CI 1.95–3.43; $p < 0.001$; Fig. 2), and the effect was similar after adjusting for pre-specified covariates (Table 3). Incorporating data past day 28, the

Table 1 Effects of prolonged methylprednisolone treatment on secondary outcomes based on individual patient data from four randomized clinical trials of acute respiratory distress syndrome

Outcome variables	Methylprednisolone ($N = 186$)	Placebo ($N = 136$)	Odds ratio (95 % CI)[a] or LSD between means (95 % CI)[b]
Died before achieving initial UAB by day 28	23 (12 %)	39 (29 %)	0.35 (0.20–0.63), $p < 0.001$[a]
Alive on day 28 on initial AB with no UAB	14 (8 %)	29 (21 %)	0.35 (0.173–0.69), $p = 0.003$[a]
Achieved initial UAB by day 28	149 (80 %)	68 (50 %)	3.77 (2.29–6.23), $p < 0.001$[a]
Returned to AB by day 28[c]	24 (16 %)	4 (6 %)	4.04 (1.31–12.43), $p = 0.015$[a]
Mechanical ventilation: free days by day 28 (mean ± SE)	13.3 ± 11.8	7.6 ± 5.7	5.76 (3.76–11.52), $p < 0.001$[b]
Duration of initial AB including data past day 28 (mean ± SD)[d]	12.9 ± 13.4	23.0 ± 13.9	−10.10 (−13.12–7.08), $p < 0.001$
Shock after study entry (mean ± SE)	6 (3 %)	20 (15 %)	0.25 (0.097–0.658), $p < 0.001$[b]
Patients with new infection after study entry (mean ± SE)	59 (32 %)	56 (41 %)	0.52 (0.311–0.857), $p = 0.011$[b]
Discharged alive from the intensive care unit by day 28	139 (75 %)	66 (49 %)	2.92 (1.802–4.72), $p < 0.001$[a]
Re-admission to intensive care unit by day 28	21 (11 %)	4 (3 %)	4.84 (1.60–14.64), $p = 0.050$[a]
Intensive care unit: free days up to day 28 (mean ± SE)	10.8 ± 0.71	6.4 ± 0.85	4.45 (2.64–6.26), $p < 0.001$[b]
Hospital: free days up to day 28 (mean ± SE)	7.0 ± 0.57	3.82 ± 0.68	3.19 (1.74–4.64), $p < 0.001$[b]
Hospital mortality	37 (20 %)	45 (33 %)	0.48 (0.29–0.81), $p = 0.006$[a]
Hospital mortality for those randomized before ARDS day 14; $n = 272$)	32 (20 %)	43 (39 %)	0.39 (0.22–0.67), $p < 0.001$[b]

Data are presented as the number, with the percentage in parenthesis unless indicated otherwise

CI Confidence interval, *LSD* Least Significant Difference test, *AB* assisted breathing, *UAB* unassisted breathing, *SE* standard error, *SD* standard deviation, *ARDS* acute respiratory distress syndrome

[a,b] Depending on the type of the response variable, we have provided either the odds ratio (OR) from the Logistic Regression Models[a], or the LSD difference between means from ordinary linear regression models, adjusting for the study effect[b]. To account for comparisons on multiple outcomes, we used a more conservative threshold of 0.001 as the significance level for these results. See ESM Table S3 for data on each trial

[c] Patients that returned to AB among the 217 patients that achieved AB by day 28. Twenty (17 methylprednisolone vs. 3 placebo) of the 28 patients belonged to the ARDS network randomized controlled trial (RCT) [9] with rapid tapering after achieving UAB

[d] Based on trial-level analysis and not stratified by study because individualized patient data (IPD) for duration of initial AB (not limited to day 28) were available only in three trials [6–8]. If based on IPD data from these three trials with IPD [6–8] and adjusted for study, the mean ± SE was 13.2 ± 2.34 vs. 22.9 ± 3.18 (mean difference −9.76, 95 % CI −16.9–−2.6; $p = 0.008$)

Table 2 GRADE summary of findings: prolonged glucocorticoid (methylprednisolone and hydrocortisone) treatment for the acute respiratory distress syndrome

Outcome	Quality assessment						Summary of findings					Certainty in evidence
							Study event rates		Relative risk (95 % CI)	Estimation of absolute effects		
	Number of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Without glucocorticoid	With glucocorticoid		Without glucocorticoid	With glucocorticoid	
Hospital mortality[a,b]	460 (4)	No serious limitations	No serious limitations	No serious limitations	Serious limitation: small number of events	Undetected	108/220 (49.1 %)	86/240 (35.8 %)	0.76 (0.59–0.98)	Mild ARDS: 27.0 % [3] Severe ARDS: 45.0 %	Mild: 6.5 % fewer (11.1 % fewer to 0.5 % fewer) Severe: 10.8 % fewer (18.5 % fewer to 0.9 % fewer)	Moderate
Duration of initial assisted breathing[c,d]	322 (4)	No serious limitations[e]	No serious limitations	No serious limitations	No serious limitations	Undetected	23.0 days	12.9 days	Mean difference −10.10 (−13.12 to −7.08)	23.0 days	10.1 fewer days (13.1 fewer to 7.1 fewer)	High
Mechanical ventilation-free days[c,d]	322 (4)	No serious limitations[e]	No serious limitations	No serious limitations	No serious limitations	Undetected	7.6 days	13.3 days	Mean difference 5.76 (3.76–11.52)	7.6 days	5.8 more days (3.8 more to 11.5 more)	High
Intensive care unit-free days[c,d]	322 (4)	Serious limitations[f]	No serious limitations	No serious limitations	No serious limitations	Undetected	6.4 days	10.8 days	Mean difference 4.45 (2.64–6.26)	6.4 days	4.5 more days (2.6 more to 6.3 more)	Moderate
Nosocomial infection[a,d]	619 (8)	No serious limitations	No serious limitations	No serious limitations	Serious limitation: small number of events	Undetected	75/281 (26.7 %)	73/338 (21.6 %)	0.77 (0.56–1.08)	26.7 %	6.1 % fewer (11.7 % fewer to 2.1 % more)	Moderate

[a] Trial-level meta-analysis by study day 28

[b] Patients randomized before day 14 of ARDS in four RCTS with $\geq$60 patients (see Fig.3)

[c] IPD meta-analysis, follow-up to hospital discharge

[d] By study day 28

[e] Although much of the data originate from RCTs with the sequential stopping rule, there was no material difference in effect estimates (and CIs)

[f] Much of the data come from RCTs with sequential design that were stopped for benefit; estimates from the traditional RCTs were smaller, but less reliable

Table 3 Time to unassisted breathing by day 28 from competing risks in regression analyses for all patients ($N = 322$) and patients randomized before day 14 of acute respiratory distress syndrome onset ($N = 272$)

Model number	Model variables	Unassisted breathing (overall)		Unassisted breathing (randomization before day 14)[a]	
		HR (95 % CI)	p value	HR (95 % CI)	p value
1	Treatment (methylprednisolone vs. placebo)[b]	2.59 (1.95–3.43)	<0.001	2.53 (1.87–3.43)	<0.001
2	Treatment, Initiation of treatment, and baseline characteristic[c]				
	Treatment (methylprednisolone vs. placebo)	2.33 (1.74–3.13)	<0.001	2.15 (1.58–2.94)	<0.001
	Initiation of treatment ([6, 7] vs. late [8, 9])	1.23 (0.88–1.72)	0.22	1.17 (0.84–1.64)	0.35
	Gender (male vs. female)	1.04 (0.78–1.40)	0.77	1.00 (0.74–1.37)	0.99
	SOFA score (>7 vs. ≤7)	0.56 (0.42–0.75)	0.001	0.59 (0.43–0.80)	0.001
	Age (>55 vs. ≤55 years)	0.65 (0.47–0.88)	0.006	0.66 (0.48–0.92)	0.015
3	Treatment, Initiation of treatment, and baseline characteristic[c]				
	Treatment (methylprednisolone vs. placebo)	2.38 (1.78–3.17)	<0.001	2.19 (1.61–2.98)	<0.001
	SOFA score (>7 vs. ≤7)	0.54 (0.41–0.72)	<0.001	0.57 (0.42–0.77)	<0.001
	Age (>55 vs. ≤55 years)	0.65 (0.48–0.88)	0.006	0.66 (0.48–0.92)	0.013

HR Hazard ratio, *SOFA* Sequential Organ Failure Assessment

[a] Compared with the overall analysis, 50 subjects in the late ARDS trials (48 in the ARDS network trial [9], and 2 in the Meduri et al. 1998 trial [6]) who were randomized after day 13 are excluded

[b] Adjusted for study stratification

[c] Baseline characteristics include age categories (≤55 and >55 years), gender, SOFA categories (≤7 and >7). The baseline characteristic data are not available from study from Rezk et al. [7] from which 27 subjects are excluded from the analysis in Models 2 to 3 ($N = 322$). The cutoff points for the age and SOFA categories were determined by the martingale residual plots from the Cox model

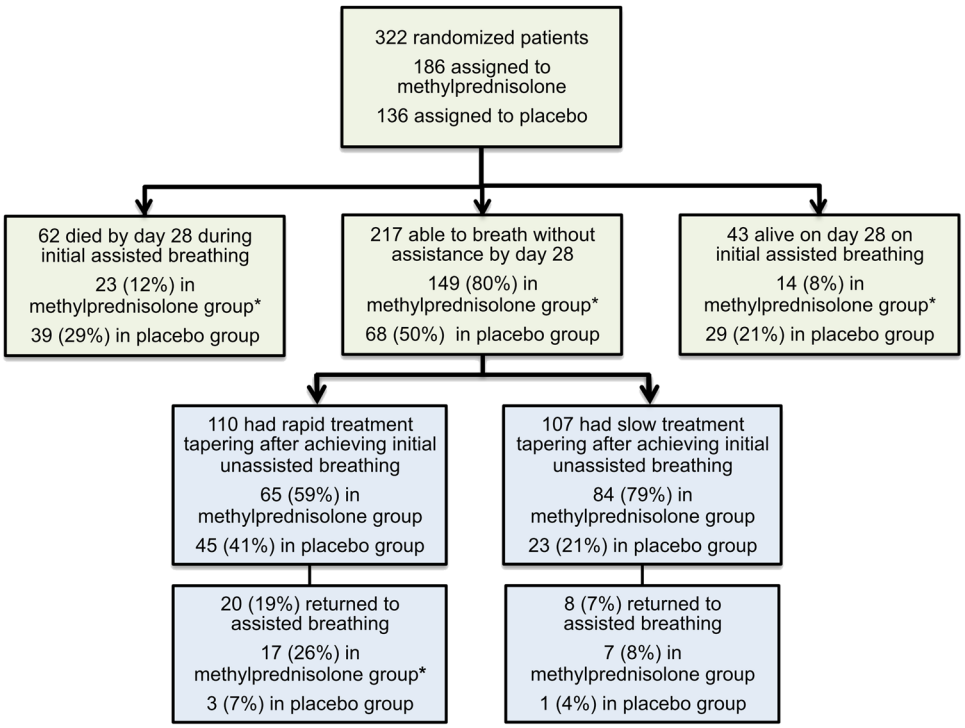

Fig. 1 Flow diagram of those who achieved initial unassisted breathing and then returned to assisted breathing in the combined dataset of methylprednisolone trials in the first 28 days of observation. *$p < 0.001$

methylprednisolone group also had shorter duration of initial AB (12.9 ± 13.4 vs. 23.0 ± 13.9 days, mean difference −10.1, 95 % CI −13.12 to −7.08; $p < 0.001$; high certainty). Timing of treatment initiation (early vs. late) was not associated with time to achieving UAB ($p = 0.22$; ESM Table S5) nor associated with methylprednisolone effect (interaction $p = 0.35$), although the benefit appeared to be greater with early initiation (ESM Fig. S2).

The ARDS network trial [9] incorporated rapid tapering of study drug after achieving initial UAB and, compared to patients in the placebo group, reported more

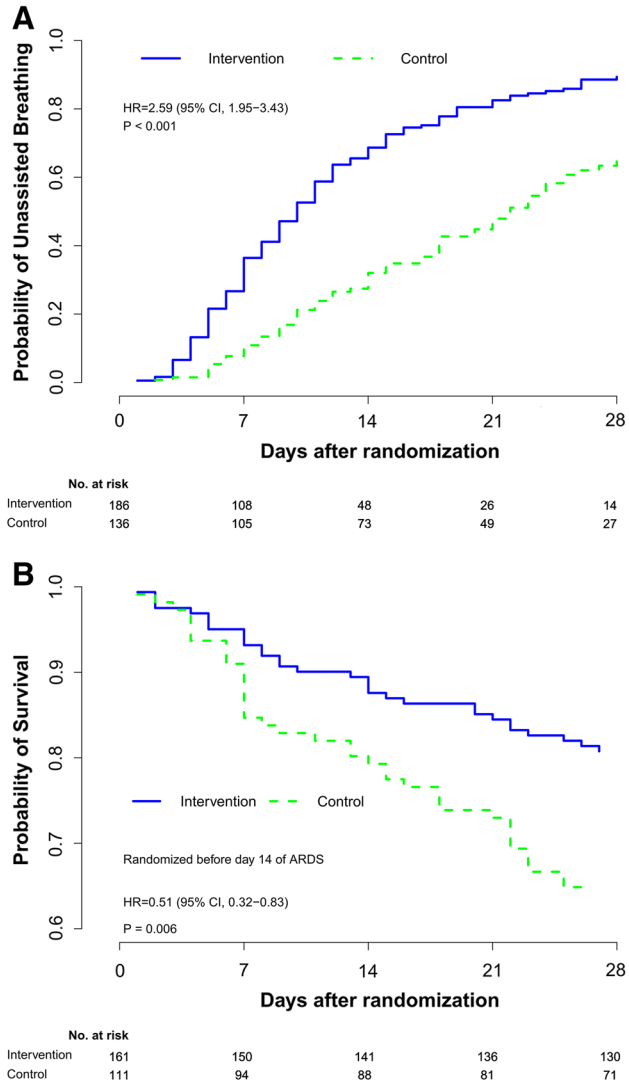

Fig. 2 Probability of achieving unassisted breathing (UAB) and survival from randomization (methylprednisolone vs. placebo) to hospital discharge or day 28. *Top* Estimated cumulative incidence of achieving (initial) UAB by day 28 for patients with acute respiratory distress syndrome (*ARDS*; $n = 322$) receiving either prolonged methylprednisolone treatment (*solid blue line*) or usual care (*dashed green line*). Death before achieving UAB is considered a competing risk. By day 28, the methylprednisolone group achieved initial UAB earlier than the placebo group [12.4 ± 0.61 vs. 19.8 ± 0.78 days; hazard ratio (*HR*) 2.59, 95 % confidence interval (*CI*) 1.95–3.43; $p < 0.001$). *Bottom* Kaplan–Meier estimates of the probability of death by hospital discharge or day 28 for patients with ARDS randomized before day 14 of ARDS onset ($n = 272$) receiving either prolonged methylprednisolone treatment (*solid blue line*) or usual care (*dashed green line*)

methylprednisolone patients returning to AB (26 vs. 7 %; $p < 0.008$) and to the ICU (21 vs. 2 %; $p = 0.007$) by day 28. In aggregate from the four methylprednisolone trials, the risk of returning to AB with rapid [9] versus slow [6–8] tapering (after achieving UAB) was 19 versus 7 % (risk difference 12, 95 % CI 2.2–21.5 %; $p = 0.02$). Reasons for return to AB and to the ICU are provided in the ESM. Hospital mortality was higher for those who returned to AB (21 vs. 4 %; $p = 0.003$).

For the secondary outcomes, the methylprednisolone group, compared to the placebo group, showed a significant increase in MV-free days in each trial [6–9] and for the aggregate dataset (13.3 vs. 7.6 days; mean difference 5.76, 95 % CI 3.76–11.52; high certainty; Table 2). The methylprednisolone group also had a significant increase in ICU-free days for three trials [6–8] and for the aggregate dataset (10.8 vs. 6.4 days; mean difference 4.45, 95 % CI 2.64–6.26; moderate certainty). Post-randomization, the methylprednisolone group had a lower rate of shock (3 vs. 15 %; $p < 0.001$) and a similar rate of infections (32 vs. 41 %; $p = 0.011$).

Prolonged methylprednisolone treatment was associated with decreased hospital mortality (20 vs. 33 %; $p = 0.006$; Table 1) and longer survival up to hospital discharge or day 28 (HR 0.62, 95 % CI 0.39–0.98; $p = 0.040$; ESM Table S4). Timing of treatment initiation (early vs. late) and speed of tapering (slow vs. rapid) were not associated with time to hospital mortality by day 28 ($p \geq 0.37$) nor with the methylprednisolone effect (interaction $p = 0.49$). In patients randomized before day 14 of ARDS, the reduction in hospital mortality was similar (20 vs. 39 %, $p = 0.003$), and the survival benefit up to hospital discharge or day 28 remained significant after adjusting for pre-specified covariates (Fig. 2; ESM Table S4). With treatment initiated before day 14, the number-needed-to-treat to save one life is 5.3. In two trials [6, 8], 19 patients (5 methylprednisolone and 14 placebo) received methylprednisolone (2 mg/kg) after failing to improve by study day 5 to 14 (cross-over). Excluding these 19 patients, hospital mortality remained unchanged in both the methylprednisolone and control group (19 vs. 30 %; $p = 0.02$).

Trial-level meta-analysis of RCTs investigating methylprednisolone and hydrocortisone treatments ($n = 619$)

We performed a trial-level meta-analysis which incorporated the results from the four RCTs in our IPD meta-analysis with four additional RCTs investigating 7 days of hydrocortisone treatment in early ARDS [11–14]. Three of these RCTs [7, 13, 14] were published after a 2009 comprehensive meta-analysis (limited to prolonged treatment) on the subject [22]. These three 'new' RCTs [7, 13, 14] did not report data on neuromuscular weakness; hence, an update meta-analysis was unnecessary. In these hydrocortisone RCTs, data were available for hospital survival and nosocomial infections in all four trials [11–14], for MV-free days in three trials [11, 12, 14], and for ICU-fee days in one trial [11]. The hydrocortisone RCTs [11–14] did not provide data on time to initial UAB

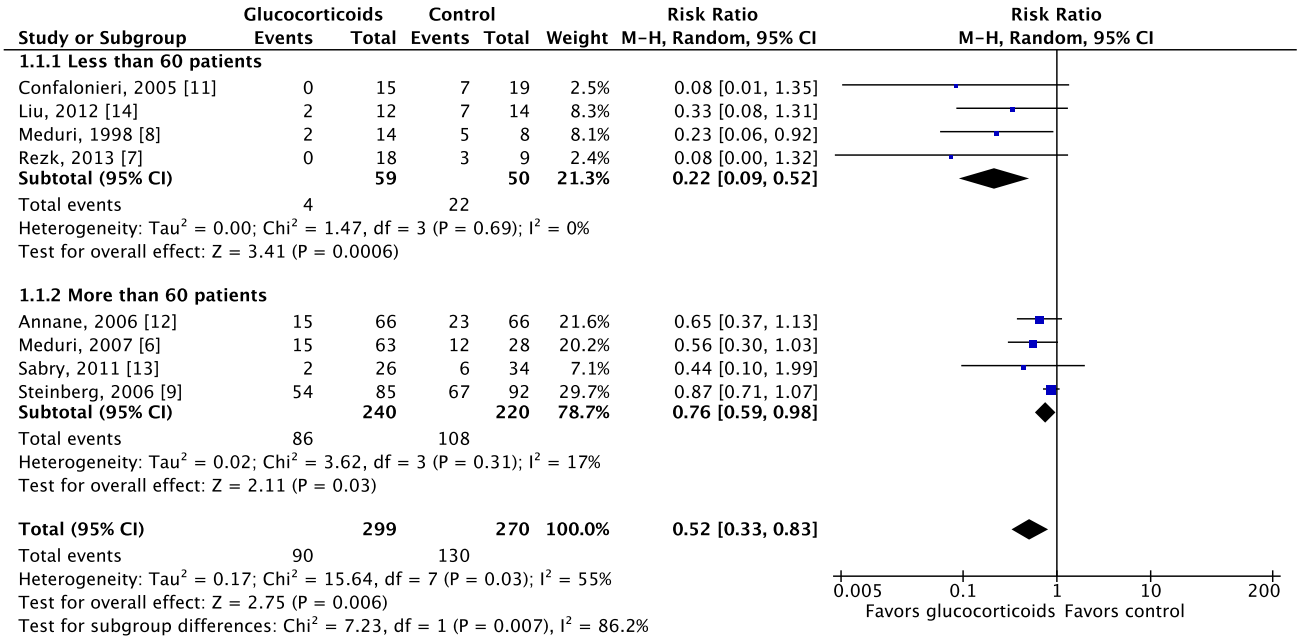

Fig. 3 Hospital mortality for patients ($n = 569$) randomized before day 14 of ARDS onset in 8 randomized trials investigating prolonged glucocorticoid treatment in ARDS. Comparison between randomized trials with <60 patients and those with ≥60 patients which investigated prolonged glucocorticoid (methylprednisolone or hydrocortisone) treatment in ARDS. *M–H* Mantel–Haenszel statistics, *df* degrees of freedom

and return to AB. Two trials were judged to be inadequately blinded (single-blind design) [7, 14], and three trials had a sequential stopping rule [6, 8, 11] (ESM Table S5).

Glucocorticoid treatment was associated with an increase in MV-free and ICU-free days (ESM Fig. S3) and with a reduced risk of in-hospital mortality for all patients (29 vs. 45 %; RR = 0.56, 95 % CI 0.36–0.87, $I^2 = 54$ %; $p = 0.009$) and for those randomized before day 14 (30 vs. 48 %; RR = 0.52, 95 % CI 0.33–0.83, $I^2 = 55$ %; $p = 0.006$; Fig. 3). In a post-hoc analysis, the ARDS network trial [9] explained almost all of the heterogeneity for mortality (excluding the ARDS network trial—RR = 0.49, 95 % CI, 0.34–0.72, $I^2 = 3$ %; interaction $p = 0.009$ vs. ARDS network trial; ESM Fig. S4). Glucocorticoid treatment was not associated with increased risk for nosocomial infections (22 vs. 27 %; RR = 0.77, 95 % CI 0.56–1.08, $I^2 = 26$ %; $p = 0.13$; moderate certainty; ESM Fig. S5).

Trials that enrolled <60 patients, when compared to trials with ≥60 patients, appeared to have a larger effect on mortality (interaction $p = 0.006$), fewer MV-free days (interaction $p = 0.02$), and fewer ICU-free days (interaction $p = 0.03$) (ESM Table S6). In all cases, we decided to trust the more conservative estimate based on RCTs enrolling ≥60 patients (36 vs. 49 %; RR = 0.76, 95 % CI 0.59–0.98, $I^2 = 17$ %; moderate certainty; Fig. 3). There were no subgroup differences based on risk of bias or other subgroups. Sensitivity analyses are provided in the ESM.

Discussion

The IPD analysis demonstrates that methylprednisolone treatment-induced downregulation of systemic inflammation accelerated resolution of ARDS, achieving sizable and significant improvements across a broad spectrum of interrelated clinical outcomes. In the methylprednisolone-treated group by study day 28, fewer patients had died before achieving UAB, more patients had achieved UAB and discharged alive from the ICU, and there was a large increase in MV-free days and ICU-free days. Initiation of treatment (early vs. late) was not associated with time to achieve UAB or time to death by hospital discharge or day 28. Rapid tapering after achieving initial UAB led to greater return to AB with partial loss of early survival benefits [10]. We also found a reduction in hospital mortality for those randomized before day 14 of ARDS onset, a finding reinforced by the trial-level meta-analysis of eight RCTs [6–9, 11–14]. In addition, prolonged glucocorticoid treatment was not associated with increased risk of developing nosocomial infections.

Our certainty in the evidence is high for duration of initial AB and MV-free days and moderate for hospital

mortality, nosocomial infections, and ICU-free days. Our certainty is limited by the inclusion of small to moderately sized RCTs with a relatively small number of events. Our analyses were also limited by the lack of IPD on baseline severity of illness in one methylprednisolone trial [7] and the lack of IPD for the hydrocortisone trials. Moreover, we could not rule out publication bias. A quarter of the data from the meta-analyses originates from three RCTs [6, 8, 11] with the sequential stopping rule, which is known to overestimate effect size [23], and some of our outcomes in the trial-level meta-analysis were not robust to sensitivity analyses, resulting in the exclusion of these studies. The major strengths of this study are: (1) the availability of IPD; (2) standardization of outcome definitions among the four methylprednisolone trials; (3) inclusion of important treatment variables (timing of initiation, duration of intervention, and speed of tapering after achieving UAB). This is the first published analysis on the impact of timing of initiation and speed of tapering on the overall response to prolonged glucocorticoid treatment in ARDS, with the limitation that this analysis of study characteristics are based on between-study comparisons, and we therefore can not rule out potential confounding of unmeasured differences between individual studies.

Duration of glucocorticoid administration is a main determinant of treatment efficacy and should be guided by two factors: (1) actual biological (not clinical) duration of the disease process (systemic and pulmonary inflammation) and (2) recovery time of the hypothalamic–pituitary–adrenal axis after discontinuing treatment [1]. Biological resolution of ARDS lags weeks behind (clinical) resolution of acute respiratory failure, a finding similar to that reported for patients with pneumonia [24]. Longitudinal measurements of inflammatory cytokines and procollagen levels in plasma and bronchoalveolar lavage in ARDS have shown that systemic and pulmonary inflammation and fibroproliferation persist for at least 4 weeks (limit of measurements), extending well beyond removal of AB [25–28]. After 10–14 days of methylprednisolone treatment, local and systemic inflammation and fibroproliferation are significantly dampened but still present (essential for disease resolution) [27, 29–31].

Importantly, even after a few days of glucocorticoid treatment, removal without tapering leads to adrenal suppression in 45 % of patients, with gradual recovery over a period of 14 days [32]. Rapid tapering of glucocorticoid treatment after achieving UAB may result in rebound inflammation and clinical deterioration (see manufacturer's product information [33]), as amply demonstrated in experimental [1, 10] and clinical literature [1, 34]. The ARDS network trial [9], in comparison to the other methylprednisolone trials [6–8], included rapid tapering of the study drug after the patient achieved initial UAB and was the only RCT with an increased rate of return to AB for the treated group. Lacking an explanation for the return to AB, we cannot confirm recrudescence of ARDS in the presence of adrenal suppression, an association commonly reported [1, 34], with rapid removal of glucocorticoid treatment. Importantly, return to AB (without reinstitution of glucocorticoid treatment) was associated with higher hospital mortality (21 vs. 4 %; $p = 0.003$), a factor recognized by the authors [9] to be an important reason why early significant physiological and survival (discharged home after initial wean: 62 vs. 49 %; $p = 0.006$ [10]) benefits did not translate into a 60-day survival (primary outcome) advantage.

Two additional methylprednisolone trials [6, 8] had individual components of the treatment protocol that affected interpretation of the findings. These trials (sequential design) [6, 8] had a longer duration of treatment and slow tapering but allowed for blinded cross-over ($n = 4$; 17 %) [8] or open-label rescue treatment ($n = 15$; 16 %) [6] for those failing to improve lung injury score (LIS) parameters by study day 5 to 14 (6 % treated vs. 39 % control). Since crossing to the other arm of the study occurred predominantly in control patients, the impact of this intervention on control survival was uncertain [22, 35, 36]. In agreement with a prior meta-analysis [22], we found that aggregate control survival was not affected by the "cross-over" design.

The ARDS network original findings [9] included an increased 60-day mortality for methylprednisolone-treated patients randomized after day 13 [9]. This subgroup ($n = 48$), however, had an uncharacteristically low mortality (8 %) and large differences in baseline characteristics [10]. When the analysis was adjusted for the imbalances at baseline, the mortality difference lost significance (25.6 vs. 13.2 %; $p = 0.325$) [36]. Irrespective of the interpretation of these data, there is a broad consensus that if glucocorticoid treatment is to be initiated, it should be initiated before day 14 of ARDS [37]. For patients randomized before day 14 of ARDS onset, in the four methylprednisolone trials, we found a 19 % absolute reduction in hospital mortality (20 vs. 39 %; $p < 0.001$) and a HR of 0.51 in time to death by hospital discharge or day 28 (95 % CI 0.32–0.83) after adjusting for SOFA score and age. While the observed mortality benefits—originating from small to moderately sized trials and investigating different treatment protocols—should be accepted with caution, concordance with the trial-level meta-analysis on hospital mortality [6–9, 11–14] (36 vs. 49 %, RR 0.76, 95 % CI 0.59–098, $I^2 = 17$ %; moderate certainty) provides increased confidence for a survival benefit for those randomized before day 14 of ARDS. This finding is further reinforced by a separate meta-analysis showing moderate certainty in a mortality reduction and in the prevention of ARDS in patients hospitalized with community-acquired pneumonia [38].

Methylprednisolone achieves a high concentration in the lung [39] and is the most frequently used intravenous

glucocorticoid for the treatment of severe acute inflammatory lung diseases [40]. Methylprednisolone has been off patent for more than 20 years, and daily treatment (based on dosage and body weight) cost approximates U.S. $2–5, making this intervention globally and equitably available. Lacking a large confirmatory trial, our analysis provides additional evidence that prolonged low-dose methylprednisolone treatment initiated early in ARDS and incorporating slow tapering to prevent rebound inflammation is associated with improved ARDS outcomes (reduces duration of MV with high certainty and mortality with moderate certainty without increased rate of infections). In early ARDS, prolonged low-dose methylprednisolone (1 mg/kg/day) treatment should be part of an integrated therapeutic strategy that may include prone position ventilation [41], short-term (48 h) paralytic agents [42], or extracorporeal membrane oxygenation [43, 44]. The findings of our study are relevant to clinical practice and to the design of future randomized trials investigating prolonged glucocorticoid treatment in ARDS, severe sepsis, and critical illness.

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Compliance with ethical standards

Conflicts of interest The authors have no competing interests to declare or any real or perceived financial interest in any product or commodity mentioned in this paper.

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