Letter

Steroid treatment for persistent ARDS: a word of caution

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Published: 12 December 2007
Critical Care 2007, **11:**425 (doi:10.1186/cc6186)
This article is online at http://ccforum.com/content/11/6/425

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Dr Meduri and colleagues, in their comment "Steroid treatment in ARDS: a highly effective treatment" [1], written in response to the article of Wajanaponsan *et al*. [2], described data and an adjusted analysis provided by the Acute Respiratory Distress Syndrome (ARDS) Network (as a personal communication). We wish to comment on their assertion of large imbalances between the treatment and steroid arms in the cohort of participants randomized after 13 days of ARDS and suggest a word of caution for interpreting this *post hoc* analysis.

Among our small subset of 48 patients randomized after 13 days of ARDS, only one of 43 baseline variables was statistically imbalanced between control and methylprednisolone (MPS) [3]. Partial pressure of arterial oxygen/fraction of inspired oxygen (P/F) ratios were similar (126 versus 128, control versus MPS). Mean age (45.2 versus 52.5) and Acute Physiology and Chronic Health Evaluation (APACHE) III (79 versus 87) were higher in the MPS group, but the differences were well within the range of random variation. When adjusted for multiple comparisons there were no statistical differences between two treatment arms.

Moreover, the lung injury score (LIS) was missing in over a third of patients and was based on compliance and P/F ratio only. We apologize for not making this apparent in our communication with Dr Meduri. The Murray LIS, which uses the number of chest X-ray quadrants and levels of positive end expiratory pressure in addition to compliance and P/F ratio, allows for missing values and is available for most patients [4]. This score was not significantly different (3.0 ± 0.5 versus 3.2 ± 0.5, $p = 0.3239$).

The adjusted analysis we provided for Dr Meduri of mortality in the subgroup of 48 patients enrolled after 13 days of ARDS was based on a set of variables derived from our prior trials and reported by us as significant for prediction of mortality in ARDS/acute lung injury (baseline APACHE III, age, plateau pressure, baseline number of organ failures, and baseline alveolar to arterial oxygen difference [A-aDO2]) [5]. With this adjustment, no statistical difference in mortality was seen between treatment arms for patients randomized after 14 days (11.2% for placebo versus 28.0% for MPS, $p = 0.57$, adjusted, compared to 12% for placebo versus 44% for MPS, $p = 0.01$, unadjusted). When the Murray LIS is added to the model, the p value is 0.22. At Dr Meduri's request, we performed a third adjustment by adding pneumonia, gender, and creatinine to the model. The results are similar to the first adjustment (mortality 13.2% for placebo and 25.6% for MPS; $p = 0.325$).

A more appropriate statistical test is a test of interaction between the onset of treatment (placebo versus MPS) and the duration of ARDS (7 to 13 days versus 14+ days). This test addresses the hypothesis that the effect of MPS is similar before and after two weeks of ARDS. Our *a priori* planned test for interaction was unadjusted and was positive ($p = 0.0170$) as reported [3]. We repeated the analysis using a logistic regression model that included treatment arm, duration of ARDS and their interaction, as well as APACHE III, age, plateau pressure, number of organ failures, A-aDO2, and the Murray LIS. The adjusted interaction p value is $p = 0.0878$. Because this is a safety issue, we still think these results provide reasons for concern for a harmful effect of MPS on mortality later in the course of ARDS.

A-aD02: alveolar to arterial oxygen difference; APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = Acute Respiratory Distress Syndrome; LIS = lung injury score; MPS = methylprednisolone; P/F = partial pressure of arterial oxygen/fraction of inspired oxygen.

In any randomized clinical trial the primary device for equalizing populations between treatment groups is random assignment of treatments, and this includes subgroups defined by pre-randomization variables. We feel that all the adjusted analyses and the *a priori* unadjusted analyses support our original concern that "starting methylprednisolone therapy more than two weeks after the onset of ARDS may increase the risk of death" [3]. The possibility of harm with late administration of corticosteroids has implications for future trials of MPS. Crossover designs where placebo non-responders receive corticosteroids later in their course may have the effect of increasing placebo mortality leading an apparent, but not necessarily real, benefit of MPS in the intention to treat (or as randomized) analysis.

Competing interests

Funded by NO1-HR 46054-64.

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