Acute respiratory distress syndrome phenotyping and latent class analysis, first steps toward precision medicine in critical care illness?

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Background

Acute respiratory distress syndrome (ARDS) in its moderate and severe forms still carries high mortality of to 30% to 40% evaluated in large observational study (1) and can be responsible for long term severe disability in survivors (2).

Since two decades, most of the advances in therapeutics came from a more comprehensive physiopathological knowledge to minimize the clinical cost of supportive care notably the ventilator induced lung injuries. Today, only two interventions are promoted by guidelines, protective lung ventilation with low tidal volume for all patients combined with early and repeated prolonged prone position in the most severe patients [e.g., partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ≤150 mmHg] (3).

Aside supportive care, numerous pharmacological interventions have been challenged in randomized clinical trial, focusing on anti-inflammatory effects [steroids, anti-tumour necrosis factor (anti-TNF), statins], anti-edema effect (B2 agonists) or anticoagulation drugs (recombinant activated protein C, thrombomodulin) (4,5).

Because ARDS is a clinical feature of very different mechanisms (sepsis, trauma, extra-pulmonary insults), because of the heterogeneity of the host response, it is not surprising that no study has found the "holy grail" to cure every patient with ARDS.

From the impressive therapeutic advances notably in onco-hematology, the emerging concept of precisions medicine, experts encouraged the conception of smart randomized trials which target subphenotype patients based on the predictive response to therapeutic, pharmacological or not, interventions.

The study of Dr. Calfee *et al.* recently published in the *Lancet* (6) is a secondary analysis of the HARP-2 study (7) using the method of latent class analysis (8). These classes were determined from the cohorts of three previous randomized controlled trial (RCT) performed by the national Heart, Lung, and Blood Institute ARDS network totalizing more than 2,000 patients (7,9,10). Based on these findings two distinct phenotypes of patients were identified. One hyperinflammatory subphenotype which represents approximatively 30% of patients is characterized by an increase of inflammatory biomarkers, a frequent and severe septic shock with metabolic acidosis and is associated with extra-pulmonary organ failures and with worse clinical outcomes. The second more frequent hypoinflammatory subphenotype is characterized with a modest increase of inflammatory biomarkers, a less incidence of septic shock and extra-pulmonary organ failures and better clinical outcomes. Interestingly, these two phenotypes have been shown to respond differently to therapeutic interventions such as positive end-expiratory pressure and fluids

management. Today, theses subphenotypes had never been challenged with a pharmacological intervention.

Therefore, on the basis of the anti-inflammatory effects of preclinical data of models of ARDS, the authors have tested the hypothesis that patients with a hyperinflammatory subphenotype of ARDS would preferentially responded to anti-inflammatory drugs such as Simvastatin.

Princeps study

The HARP-2 trial was a multicenter randomized study performed in 40 intensive care units of the UK and Ireland which enrolled patients within 48 h of the onset of ARDS, defined by a PaO_2 to FiO_2 $\leq$300 mmHg. Patients were randomly assigned (1:1) to receive daily 80 mg of simvastatin or placebo until day 28, discharge from intensive care unit (ICU), death or development of a contraindication to pursuit statin therapy. Randomization was stratified in each site according to the presence of shock with vasopressor requirement. The primary outcome was the number of ventilator free days (VFD) in each group. Secondary outcomes were non-pulmonary organ failure-free days and mortality. No difference in any of these outcomes were attempted by the HARP-2 study. For ancillary studies, two pro-inflammatory biomarkers interleukin 6 (IL-6) and soluble tumour necrosis factor receptor 1 (sTNFr1) were measured in duplicate and stored at –80 ℃.

Latent class analysis

From the princeps study, aside the two biomarkers, predefined clinical and biological variables were implemented, namely, age, ARDS risks factors, bilirubin and creatinine values, platelet count, tidal volume (Vt), Plateau pressure (Pplat) and PaO_2 to FiO_2 ratio to perform latent class analysis. Variables outcomes were not included in the model. Estimated models varied from one to four classes from whom the best fit used a two-class model. To estimate model parameters, each continuous variable was placed on a z-scale with a mean of 0 and SD of 1. Interaction between treatment and class assignment was tested for mortality and VFD. These two outcomes were also tested by a competing risk analysis.

Main results and strengths of the study

From the HARP-2 study, 353 (65%) patients and 186 (35%) patients were respectively assigned in the hypoinflammatory

subphenotype (class 1) and in the hyperinflammatory subphenotype (class 2). In class 1, 175 (50%) patients were randomized to simvastatin and 84 (45%) patients in class 2. In this latter class, patients were older and had more frequently an indirect ARDS risk factor (73%) than in the class 1 (39%). Whereas the HARP-2 study found no difference in 28-day survival in the whole population, stratification by treatment (placebo or simvastatin) and subphenotype (class 1 or class 2) showed different 28-day survival curves (P<0.0001). In particular, 28-day mortality was 32% (27 of 84) in the hyperinflammatory subphenotype patients treated with simvastatin as compared with 45% (46 of 102) in the hyperinflammatory subphenotype patients treated with placebo. In contrast, 28-day was not different in the hypoinflammatory subphenotype patients treated or not with simvastatin, respectively 16% and 17%. Survival rate was also higher at 90 day, in the class 2 patients treated with simvastatin as compared to those treated with placebo.

Conversely and contrary to the princeps study, when stratified by subphenotype and treatment, time to unassisted breathing differed significantly between groups. However, this difference did not reach significance between patients in class 2 treated with placebo or with simvastatin. In class 2 patients, median VFD were 7 days [interquartile range (IQR) 0–18] in the simvastatin arm *vs.* 0 (IQR 0–17) in the placebo arm.

The secondary subphenotype analysis of the HARP-2 study highlights two major findings. First, with a limited subset of clinical and biological data, the study confirmed two different patterns of ARDS patients with different clinical trajectories. The two class subphenotypes are consistent across geographical sites and are robust whatever the specific data collected allowing generalization of previous studies. Second, these phenotypes have different response to pharmacological intervention with simvastatin suggesting that interventions might be driven by the appurtenance to the hypoinflammatory subphenotype or the hyperinflammatory subphenotype. Moreover, the hyperinflammatory subphenotype patients randomly assigned to simvastatin were the more susceptible patients to benefit from presumed mechanism of action of statin in ARDS. Thus, biological plausibility has been transformed in these patients in clinical outcome, reinforcing the result. Interestingly, as previously described, the surrogate parameters of extra pulmonary organ failure had more ability to differentiate the two phenotypes than pulmonary-specific parameters, probably by the fact that inclusion criteria in the HARP-2 study were mostly based on

pulmonary function tests and by the fact that the same common ventilator management protocol was used in all patients.

Unresolved issues

Whether the 28-day survival rate is greater in the hyperinflammatory subphenotype treated with simvastatin as compared with those treated with placebo, contrasts with the lack of effect of time to unassisted breathing observed in the two groups. Aside the possible lack of power of the latent class analysis which was not planned in the original trial design, the authors may not rule out caveats regarding subgroup analysis with unmeasured confounders that could have contributed to theses discrepancies. As underlined by the authors, the secondary analysis does not replace a prospective randomized study of simvastatin targeting ARDS patients with class 2, hyperinflammatory subphenotype.

ARDS phenotyping, enrichment analysis and smart future randomized clinical trials

So, what is the next step? After decades of negative pharmacological trials, the second analysis of the HARP-2 study suggests that a subphenotype of hyperinflammatory ARDS patients might benefit from a targeted pharmacological anti-inflammatory intervention with statin therapy.

More than the results of the present study, it suggests a smarter way to design studies in critical care illness for ARDS as well as for sepsis (11). Indeed, to counteract the heterogeneity of ARDS, the identification of subgroups of patients may be useful to propose intervention for patients with a higher risk of mortality (prognostic enrichment), either for patients with differences of susceptibility responses in treatment arms (predictive enrichment) (12).

The first step could be to focus on the hyper inflammatory sub phenotype mainly associated with infection, the most common ARDS risk factor. First, through a large prospective observational cohort study with comprehensive biology, to select a limited number of interest biomarkers (transcriptome, proteome) associated with clinical features and/or prognosis, second to design a prospective randomized trial with assignation of a pharmacological intervention according to a high probability of response (biomarkers expression).

To summary, results of latent class analysis studies

open perspectives to precision medicine with personalized decision-making process (13). Futures studies and results of ongoing studies are expected (14,15).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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