Pharmacotherapy for Adult Patients with Acute Respiratory Distress Syndrome

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Acute respiratory distress syndrome (ARDS) is one of the leading death reasons in Intensive Care Unit (ICU).[1] It is frustrating that there is no pharmacotherapy effective enough to reduce the mortality of ARDS. The most important treatment of ARDS nowadays is supportive treatment, including mechanical ventilation (MV), fluid management, and sedation.[2] Successful trials of ARDS treatments usually aim to avoid further lung injury of ARDS patients, such as low tidal volume of MV and conservative fluid strategy. These strategies can only maintain the mortality around 40%.[1]

It is a matter of urgency to develop new methods for the treatment of ARDS. There are plenty of trials focusing on medication treatment for ARDS patients. Some medicines have been proved to be beneficial for certain kinds of ARDS including novel agents and newly developed medication. Besides, results from some early trials should be re-evaluated because of the evolution of diagnostic criteria of ARDS.[3]

Classically, ARDS is recognized to be an inflammatory lung injury. The use of corticosteroid as an anti-inflammatory agent should be a perfect match for the treatment of ARDS. However, results from randomized, placebo-controlled clinical trials (RCTs) showed that there are no benefits from corticosteroids for the improvement of ARDS survival. On the other hand, some clinical data implied that corticosteroids were able to increase oxygen level,[4] MV-free days,[5] and ICU-free days,[4] which suggested that corticosteroid could play an important role during the treatment of ARDS. The problem is how and when to use it. Due to significant heterogeneity of all the trials, it is hard to come to a definitive recommendation.

It is proved that low dosage of corticosteroid for ARDS patients led to better outcome. Tang *et al*.[6] performed a meta-analysis consisting of five cohort studies and four trials that used 0.5–2.5 $mg \cdot kg^{-1} \cdot d^{-1}$ of methylprednisolone or equivalent to treat acute lung injury (ALI)/ARDS. Both cohort studies and trials showed a trend toward mortality reduction (overall relative risk: 0.62, 95% confidence interval: 0.43–0.91, $P = 0.01$). Besides, methylprednisolone also improved gas exchange, MV-free days, ICU-free days, Multiple Organ Dysfunction Syndrome Score and Lung Injury Scores. Complications such as infection and neuromyopathy were not increasing in corticosteroids group.

Another notice of corticosteroid use is timing and duration. ARDS patients may benefit from corticosteroid when initiation of the medicine at early stage of the syndrome. Meduri *et al*.[4] conducted a RCT including ninety-one patients with early ARDS (<72 h) randomized (2:1 fashion) to methylprednisolone group (1 $mg \cdot kg^{-1} \cdot d^{-1}$) and placebo group. They found that corticosteroid group (63 patients) had lower ICU mortality (20.6% vs. 42.9%, $P = 0.03$) and better gas exchange, more ICU-free days and MV-free days without increased risk of complications. The number of the sample was too small to be convincing. Later on, Meduri *et al*.[7] performed a meta-analysis of four trails investigating methylprednisolone treatment and a trial-level meta-analysis incorporating four additional RCTs investigating hydrocortisone treatment in early ARDS to support this idea. It was found that by day 28, methylprednisolone group

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had better outcome including lower mortality (20% vs. 33%; $P = 0.006$), more ICU-free days and MV-free days. Another finding of the trial-level meta-analysis was that patients who received hydrocortisone treatment before day 14 of ARDS onset had better survival. There are evidences supporting this conclusion. Subgroup analysis of a large-scale RCT also indicated 60-day (35% vs. 8%) and 180-day mortality (44% vs. 12%) increased in corticosteroid group when randomized after 14 days of the onset of ARDS while both of the two time point mortality decreased when patients were randomized between day 7 to day 13 after the onset of ARDS, but without statistically significant.[5] According to these data mentioned above, corticosteroid administration to ARDS patients is recommended at a low dosage before day 14 of ARDS onset.

Why do the timing and duration matter during the treatment of corticosteroid in ARDS patients? We believed that it is because the inflammatory response of host is constantly changing through the whole stage of ARDS. Corticosteroid is aim to suppress the excessive reaction of immune system. Theoretically, the high level of immune response occurs during the early stage of inflammatory disease.[8] However, we do not have an effective way to test the level and duration of immune response. The reason for why some patients of early ARDS do not benefit from the use of corticosteroid could be that the immune response may already be regulated to a low level by the host system. Torres *et al*.[9] used serum C-reactive protein level >150 mg/L as a marker of high inflammatory response of severe community-acquired pneumonia (SCAP) patients. It turned out that corticosteroid treatment was associated with less treatment failure among patients with high level immune response. Although this trial was not about ARDS, it suggested that there is certain kind of patients who will benefit from the treatment of corticosteroid. Since the connection of SCAP and ARDS is tight, the next stage trials may focus on looking for a marker to label this kind of patients who will benefit from the use of corticosteroid.

It is difficult to stop ARDS after it is fully established. It may be wise to focus on early identification of patients at risk and timely implementation of prevention therapy. Statins and aspirin are the two kinds of most studied medicine to prevent patients at high risk from turning into ARDS. Statins are proved to have the effects of immunomodulatory and anti-inflammatory which can be used against ARDS. Shyamsundar *et al*.[10] recruited 20 healthy volunteers pretreated with simvastatin before lipopolysaccharide (LPS) inhalation. After LPS challenge, cytokine levels were significantly reduced both in bronchoalveolar lavage (BAL) and plasma. As for critically ill patients, they were less likely to develop ALI/ARDS if pretreated with statins.[11] Moreover, statin therapy might be able to reduce mortality and increase MV-free days in ALI/ARDS patients.[12] However, high quality randomized controlled trial showed neither mortality reduction nor clinical outcome improvement of statins treatment after ARDS onset.[13] Meta-analysis of 13 studies also demonstrated that patients were not able to benefit from the use of statins as preventative agent or treatment medicine.[14] Hence, the effects of statins on the prevention and treatment of ALI/ARDS are still controversial.

Animal experiments revealed that platelets were essential for the development of ALI. Aspirin, as an antiplatelet agent, was found to be able to prevent the development of lung injury and prevent mortality in a transfusion-related ALI mice model.[15] However, the Lung Injury Prevention Study With Aspirin study, a large-scale RCT,[16] demonstrated that use of aspirin could not reduce the risk of ARDS among at-risk patients. The limitation of this study was that the actual rate of ARDS was lower than the expected rate (9.5% vs. 18%). That might explain why no effects on the primary clinical outcomes are noted. To date, there are inadequate evidence for physicians to consider aspirin as a preventative therapy.

Inhalations can be an ideal way to deliver medicines direct to lungs with less systemic side effects which are commonly used for respiratory diseases. The most widely used inhaled medications are beta-agonist. Alveolar-capillary barrier is damaged during ARDS leading to the increase of alveolar fluid. Beta-agonists are proved to have the ability to accelerate the rate of alveolar fluid clearance in *ex vivo* human lung which might be a breakthrough of ARDS treatment. Perkins *et al*.[17] evaluated inhaled short-acting beta-agonists (salmeterol) for ARDS prevention among patients undergoing esophagectomy. Although there was no difference of incidence of ARDS between treatment group and control group, salmeterol was associated with less frequent adverse events and reduction of alveolar inflammatory biomarkers. The latest outcome of a phase II trial, Lung Injury Prevention Study With Budesonide and Beta,[18] demonstrated that the oxygen saturation benefited from a combination of a long-acting inhaled beta-agonist agent (formoterol) and an inhaled steroid (budesonide) administrated to adult patients at risk for ARDS. The treatment group also showed a low incidence of developing ARDS and requiring MV. The result supported further study to test the efficacy of the combination of inhaled corticosteroids and beta agonists for prevention of ARDS.

There are other agents which have been tested. The p38 mitogen-activated phosphor kinase (MAPK) is the key protein kinase which regulates the production of inflammatory cytokines and chemokines. Inhibition of p38 MAPK as a clinical treatment has been proved to be effective to decrease inflammatory biomarkers in respiratory diseases such as COPD.[19] A phase IIa RCT of p38 MAPK inhibitor has been conducted in patients with major trauma at risk for developing ARDS.[20] The drug was well tolerated and capable of reducing the plasma level of inflammatory markers. Besides, patients treated with the medicine were less likely to develop ARDS. The p38 MAPK inhibitor may be expectable as a pharmacal solution to ARDS. Keratinocyte growth factor (KGF) improved ATII cell barrier function which led to reduction of epithelial injury and promotion of ARDS recovery.[21] Shyamsundar *et al*.[22] pretreated volunteers with KGF before LPS challenge. BAL

investigation showed KGF improved alveolar epithelial proliferation by increasing surfactant protein D. The trial also found the influence of KGF on innate pulmonary immunity through its enhancement macrophage clearance ability, which was granulocyte-macrophage colony-stimulating factor (GM-CSF) dependent. It revealed the possibility of GM-CSF as an intervention for ARDS patients. Like other pharmacological agents, GM-CSF did not show a clinical efficacy to increase MV-free days and survival rate in a Phase II trial.[23] Large-scale trials are needed for advanced evidence.

There are some reasons why almost every pharmacologic therapy has failed in clinical trials of ARDS despite their experimental and preclinical data were quite promising. As we all know, ARDS can be triggered by various clinical situations such as sepsis, pneumonia, aspiration, trauma, blood transfusion, and so on. The underlying pathophysiology of each disease is numerous. It is quite difficult for a single medicine to cover them all and change the outcome of all ARDS patients. Besides, ARDS patients usually have mixed conditions, most of which are extreme critical and cannot be improve by one kind of medication only. Most ARDS patients have dynamic instability, especially in lung circulation, which may cause the impediment of drug delivery to the damaged area of lungs.

After all, we believe that the most important reason is that the diagnostic tools of ARDS are still based on clinical findings and can be mistaken by many other clinical conditions. It is reported that nearly half of the ARDS patients who met the clinical criteria do not have the specific pathological changes of ARDS.[24-26] Berlin definition is helping to rule out unqualified patients who used to be diagnosed as ARDS patients and were enrolled in ARDS trials.[3] More specific markers are needed for early diagnosis of ARDS, or otherwise to distinguish the subphenotype of ARDS which might be able to benefit from certain medications. New agents are also needed to target key factors of specific pathways.

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Conflicts of interest

There are no conflicts of interest.

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