

Intravenous Interferon Beta-1a for Acute Respiratory Distress Syndrome Treatment in Intensive Care Unit

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Normally, pulmonary function requires dry pulmonary alveoli located closely to perfused blood capillaries to target sufficient gas exchange. Normal lungs contain approximately 480×10^6 alveoli. The pulmonary capillary endothelium allows serum protein to stay intravascular and to hold back fluids by oncotic pressures, thus can control the balance between fluids by selective permeable membrane of the pulmonary capillary endothelium. The small amounts of fluid are reabsorbed by the oncotic gradient of the pulmonary interstitial lymphatic system. Acute respiratory distress syndrome (ARDS), a serious clinical pulmonary disorder occurs following various severe pulmonary insults, including major pulmonary trauma, non-pulmonary sepsis, gastric content aspiration, and pneumonia. ARDS, a type of acute diffuse lung injury, contributes to releasing pro-inflammatory cytokines, such as interleukin (IL)-1 beta (IL-1 β), IL-6, IL-8, and tumor necrosis factor alpha (TNF- α), that in turn recruit the components of the innate immune system. Neutrophil activation produces toxic mediators, such as protease damaging the pulmonary capillary endothelium and pulmonary alveolar epithelium and reactive oxygen species (ROS). Progressively, these proteins can effuse from the vascular space, that results in the loss of the oncotic pressure gradient between pulmonary alveolar capillaries and the air space and facilitating the progress of the fluid into the pulmonary interstitium and air space. This protein-rich fluid inactivates pulmonary alveolar surfactant and results in pulmonary alveolar collapse, impairment of gas exchange, increased dead space, decreased carbon dioxide (CO₂) elimination, increased pulmonary vascular permeability and reduced lung compliance. Finally, these pathophysiological mechanisms lead to acute respiratory failure. Sepsis-induced ARDS can initiate the epithelial side (direct lung injury) or the endothelial side (indirect lung injury).

An infection originating in the lung, such as pneumonia (barrier dysfunction) can arise from sepsis-induced ARDS. Intraabdominal infection can arise from sepsis-induced ARDS. The ARDS mortality remains high at about 20% to 40% across all ARDS severities (mild (Partial Pressure of Oxygen (PaO₂)/Fraction of Inspired Oxygen (FiO₂) > 200 - 300 mmHg or less with Positive End-Expiratory Pressure (PEEP) or Continuous Positive Airway Pressure (CPAP) 5 cmH₂O or higher); moderate (PaO₂/FiO₂ > 100 - 200 mmHg or less with PEEP 5 cmH₂O or higher), and severe (PaO₂/FiO₂ 100 mmHg or less with PEEP 5 cmH₂O or higher), The Berlin Definition of ARDS). ARDS patients consume critically more resources compared to other critically ill-patient groups due to longer hospital and intensive care unit (ICU) stays. Approximately, 35% of moderate or severe ARDS patients are unable to return to work 24 months after hospital discharge.

Most ARDS patients usually are applied with invasive mechanical ventilation (IMV) to provide sufficient pulmonary ventilation and issue oxygenation. IMV can damage the injured lung "ventilator-induced lung injury (VILI)" that is classified into three major aspects: 1) biotrauma, 2) atelectrauma and 3) volutrauma/barotrauma. Interferon beta-1a, an interferon beta-1 agonist with ability to up-regulate CD73, a molecule which yields anti-inflammatory adenosine, which enhances endothelial barrier function and contributes to the preven-

tion of vascular leakage that predominantly occurs in ARDS. A previous study on 37 patients with ARDS and 59 controls demonstrated that interferon beta-1a increased the number of CD73-positive blood vessels in lung culture by four times on day 1 ($p = 0.04$) and by 14.3 times by day 4 ($p = 0.004$). The optimal tolerated dose of interferon beta-1a in this study was 10 μg per day, once daily for 6 days. By day 28, treatment outcome was associated with an 81% reduction in odds of 28-day mortality (odds ratio = 0.19 (95% Confidential Interval (CI): 0.03 - 0.72), $p = 0.01$). Nevertheless, another recent study on 144 ARDS patients and 152 controls by intravenous administration of 10 μg per day, once daily for 6 days revealed that there was no significant difference in 28-day mortality between the interferon beta-1a and control groups (26.4% versus 23.0%; difference, 3.4% (95% CI: -8.1% to 14.8%); $p = 0.53$). Seventy-four ARDS patients (25.0%) experienced adverse events related to treatment during the study (41 ARDS patients (28.5%) in the interferon beta-1a group and 33 (21.7%) control subjects).

In conclusion, further studies on intravenous interferon beta-1a treatment in larger number of ARDS patients are urgently needed to prove the efficacy of the interferon beta-1a.

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