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Acute lung injury and sepsis pharmacology

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ABSTRACT

One of the main causes of death in sepsis is acute lung damage (ALI) linked to the condition. As a result, numerous pharmacological and nonpharmacological techniques have been used to slow its progression. Few of these tactics have actually been successful. The epidemiology and pathophysiology of ALI, frequently used pharmacologic and nonpharmacologic treatments, and novel therapeutic modalities that are anticipated to be the subject of future trials are all covered in this article.

Keywords: Acute lung injury; Sepsis; Pharmacology; Immune response; Cytokines; Epidemiology; Anti-inflammatory agents

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INTRODUCTION

Acute lung damage (ALI) brought on by sepsis is a significant cause of morbidity and mortality in both adult and paediatric populations, as well as a significant financial burden on intensive care units (ICUs). The two most common aetiologies of ALI and acute respiratory distress syndrome (ARDS), respectively, are sepsis and pneumonia. Numerous therapeutic approaches have been tried to slow the progression of ALI since ARDS is linked to a risk of mortality of 26-44% in the adult population and 22% in the paediatric population. While the pharmacology of ALI in sepsis will be the main emphasis of this study, it will also provide brief reviews of nonpharmacologic therapy options. Unless treatments are only available to people with ARDS, the term "ALI" will be used to describe both ALI and ARDS [1].

ALI should be viewed as a syndrome rather than a disease since, like sepsis, it is a clinical description and shared endpoint of numerous pathophysiologic processes. Clinicians strive to treat these common processes associated with ALI, address the underlying etiologic causes, and, when practical, customise treatment to a particular underlying disease. Exudative, proliferative, and fibrotic are the three stages in which ALI traditionally has been regarded as developing. The severity and duration of these stages are greatly influenced by various mechanisms of lung injury and the seriousness of illnesses, but the three-stage model has mostly held true for four decades and provides a good framework for discussion [2].

The first stage of ALI, known as exudative, lasts for the first seven days of the disease and is characterised by a net efflux of proteinaceous material into the alveolar spaces. According to definition, this efflux is associated with an increase in capillary permeability (i.e., a decreased reflection coefficient) rather than hydrostatic pressures (i.e., a raised left atrial pressure). Because the exudate is more viscous than air and because pulmonary surfactant is neutralised, the alveolar exudate decreases lung compliance and raises alveolar surface tension. Lung compliance is variable due to varied degrees of vascular leak, resulting in focal areas of atelectasis and the typical patchy bilateral infiltrate on chest X-rays of ALI. This diverse lung compliance causes relative overdistention of more normal alveolar units and underinflation of lower compliance ones during positive pressure breathing. The hypoxemia of ALI is caused by the perfusion of lung units with insufficient ventilation, which causes pulmonary venous desaturation [3].

Three procedures together referred to as the "Lung Protective Strategy" are meant to reduce subsequent lung injury in ALI patients who need mechanical ventilation. Tidal volume reduction (volutrauma), airway pressure

reduction (barotrauma), and administration of the minimal end expiratory pressure to prevent airway collapse (atelectrauma) are these therapies. According to a significant multicenter trial on ARDS, mortality decreased by 9% with a 6 mL/kg tidal volume compared to a 12 mL/kg volume. There is little evidence that using oscillatory ventilation, high PEEP-low fractional inspired oxygen, or novel ventilator modes like airway pressure release ventilation can reduce mortality. Other ventilator modes like neutrally adjusted ventilator assist (NAVA) or volume support ventilation do not have mortality data, despite the fact that these and other modes have improved secondary outcomes like oxygenation, the length of mechanical ventilation, or patient-ventilator synchrony [4].

Numerous studies have examined the use of corticosteroids for ALI, one of which being a multicenter randomised study. Their usage is justified therapeutically by their ability to reduce fibro growth. There have been several reported dosing regimens for corticosteroids, but in the largest experiment, the dosage was 2 mg/kg of Solu-Medrol as a loading dose, followed by 0.5 mg/kg every 6 hours for 14 days, 0.5 mg/kg every 12 hours for 7 days, and then a taper based on the patient's clinical condition. In the aforementioned trial, the intervention group saw increases in oxygenation and days without a ventilator but not in death [5].

On subset analysis, there was a tendency for improved mortality in patients treated 7–14 days after the onset of ARDS, but there was a significantly higher risk of death in patients given solumedrol more than 14 days after the onset of ARDS. A meta-analysis of patients who received corticosteroid treatment before day 14 revealed better results. Within 72 hours of the onset of ARDS, corticosteroids may be beneficial, according to a trial by the same authors. There have been no studies done to compare drug delivery timing, dosage, or duration. Early, high-dose steroid therapy, particularly in sepsis, may impede pathogen clearance, cause myopathy, raise the risk of subsequent infections, and hinder wound healing. The use of corticosteroids in ALI before 14 days after ALI start is supported by the literature. A thorough risk-benefit analysis should be conducted before considering their use in this situation [6].

DISCUSSION

The disruption of circadian rhythm has been linked to a number of disorders, including cancer, inflammation, and metabolic dysregulation. As a result, pharmacological modulation of circadian genes is a potential treatment strategy for these conditions. Rev-Erb, a heme-binging repressor, controls inflammation, metabolism, and circadian rhythm. Studies on mouse colitis have demonstrated that dextran sulphate sodium-induced inflammation is suppressed by pharmacologically activating Rev-Erb. Uncertainty persists regarding the connection between Rev-Erb and the ALI inflammation brought on by sepsis. In order to understand how Rev-Erb affects ALI, this work used a murine endotoxemic model that was produced by the administration of LPS [7].

In this study, pro-inflammatory cytokine IL-6 and TNF- production caused by LPS was found to be down regulated by SR9009, whereas IL-6 and TNF- expressions were found to be upregulated by Rev-Erb knockdown, which is consistent with prior studies on the inhibitory effect of Rev-Erb on the transcription of IL-6. As anticipated, the inflammatory response caused by LPS in RAW246.7 was reduced by the pharmacological activation of Rev-Erb via SR9009. We also confirmed the mechanism underlying Rev-Erb's impact on the inflammatory response following SR9009 activation.

It has been demonstrated that SR9009 inhibits dextran sulphate sodium (DSS)-induced colitis in wild-type mice, but not in Nlrp3-/- or Rev-Erb-/- mice. They established that Rev-Erb controls experimental colitis via suppressing the NF-B/Nlrp3 axis. In our work, we found that LPS-treated RAW246.7 had higher levels of TLR4 expression and NF-B phosphorylation. TLR4 expression and NF-B phosphorylation were lower in the SR9009+LPS group than they were in the LPS group. We hypothesised that SR9009 reduced the expression of proinflammatory cytokines through the TLR4-mediated NF-B pathway, hence inhibiting RAW246.7's inflammatory response [8].

Additionally, pre-treatment with an injection of SR9009 could greatly reduce the inflammatory and histological alterations brought on by LPS as well as decrease the rise in LPS-induced levels of oxidative stress in the lung. Additionally, SR9009 injection effectively reduced arterial $PaCO_2$ and LD concentration while increasing arterial PaO_2, SO_2, HCO_3-, and blood pH to alleviate acidosis and hypoxemia. The protective effect of SR9009 injection in ALI is confirmed by our data, which indicate Rev-Erb may lessen inflammatory cell sequestration and migration into lung tissue. The LPS-treated group, however, elevated the expression of IL-10, while the SR9009 pre-treated group was able to inhibit the expression of IL-10, according to both in vitro and in vivo research.

A strong anti-inflammatory agent called IL-10 controls the overproduction of inflammatory cytokines when there is an infection or tissue injury. In response to TLR signalling, macrophages are a significant source of IL-10, which is produced as a feedback mechanism to reduce inflammatory response. Activation of TLR4 by LPS induces the expression of IL-10 through the sequential induction of type I IFNs, followed by induction and signalling through IL-27, which may be related. Following pre-treatment with SR9009, IL-10 expression was suppressed, which is consistent with earlier studies showing that Rev-Erb both directly and indirectly controls its expression.

We've already established that Rev-Erb regulates inflammation in LPS-induced RAW246.7 cells in a test tube. Therefore, we assume Rev-Erb will function the same way in ALI mice. Leukocytes are activated in the circulation during sepsis, and some of them settle in the pulmonary microcirculation. Increased lung leukocyte build-up is a result of the condition's progression. Following their migration into the pulmonary interstitium, these leukocytes cause tissue edoema and disruption of gas exchange by increasing capillary permeability. After administering LPS

to the ALI mice employed in this investigation, we saw a sizable leukocyte infiltration and pulmonary edoema in the lung tissue [9].

Proinflammatory cytokines, including as IL-6 and TNF-, are crucial in ALI, A worse patient outcome is linked to persistent increase of proinflammatory cytokines in ALI or sepsis. In this work, we discovered that LPS treatment enhanced the expression levels of IL-6 and TNF- in both serum and lung tissues. In addition, lung tissues from mice with sepsis caused by LPS had an elevated W/D ratio. Rev-Erb, on the other hand, has the ability to successfully counteract the rise in the ratio of W/D in lung tissue as well as the elevation in the expression of the proinflammatory cytokines IL-6 and TNF. In this work, SR9009 pre-treatment decreased the expressions of MDA, LA, and SOD, which were upregulated in LPS-induced sepsis mice. MDA can indirectly reflect the degree of cell damage and directly reflect the degree of lipid peroxidation in the body. In LPS-induced sepsis mice, Rev-Erb decreased the expression of MDA, LD, and SOD while boosting T-GSH levels.

Additionally, arterial blood gas measurement in LPS-treated mice showed hypoxia and acidosis, showing lung respiratory failure compatible with the clinical signs and pulmonary lesions of ALI. These results showed that the LPS mouse model accurately simulated ALI. Rev-Erb-specific agonist SR9009, a synthetic pyrrole derivative, has potent in vivo effects on metabolism and cardiac ischemia-reperfusion. We inferred from this finding that SR9009 injection would be useful in the management of ALI. According to the results of this investigation, pre-treating the lungs with SR9009 could greatly reduce the inflammatory and histological alterations that LPS causes. Additionally, SR9009 pre-treatment effectively reduced arterial $PaCO_2$ and increased arterial PaO_2, SO_2, HCO_3- concentration, and blood PH to alleviate acidosis and hypoxemia. The aforementioned results support Rev-Erb's protective role in ALI and imply that it may lessen inflammatory cells' sequestration and invasion of lung tissue [10].

CONCLUSIONS

Sepsis frequently leads to ALI complications. Despite numerous trials, only the use of a low tidal volume breathing approach has proven to be clearly beneficial in terms of mortality reduction. Even though no mortality benefit could be shown, a restrictive fluid strategy has strong backing. Perhaps just two medications—solumedrol and furosemide—have demonstrated therapeutic value. The additional therapies on the list, while not recommended for general use, might help some people. ALI cannot currently be phenotype in a clinically significant manner. Despite a lengthy history of failures, researchers will continue to look into new pharmacologic and nonpharmacologic therapy because ALI is a prevalent occurrence in ICUs and is linked to high morbidity, mortality, and cost.

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None

CONFLICT OF INTEREST

None

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