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Timing of valproic acid in acute lung injury: prevention is the best therapy?

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ABSTRACT

Background: Acute lung injury and respiratory distress syndrome is characterized by uncontrolled inflammation of the lungs after a severe inflammatory stimulus. We have previously demonstrated an ameliorated syndrome and improved survival in mice with early administration of valproic acid (VPA), a broad-spectrum histone deacetylase inhibitor, while studies in humans have shown no benefit when anti-inflammatories are administered late. The current study tested the hypothesis that early treatment would improve outcomes in our gram-negative pneumonia-induced acute lung injury.

Materials and methods: Mice (C57BL/6) had 50 × 10^6 *Escherichia coli* (strain 19,138) instilled endotracheally and VPA (250 mg/kg) administered intraperitoneally 3, 4, 6, and 9 h ($n = 12$/group) later. Six hours after VPA administration, the animals were sacrificed, and bronchoalveolar lavage (BAL) fluid interleukin-6 (IL-6), tumor necrosis factor, neutrophils and macrophages as well as the *E coli* colony-forming units were quantified. Plasma IL-6 was also measured. A separate group of mice ($n = 12$/group) were followed prospectively for 7 days to assess survival.

Results: BAL IL-6 and tumor necrosis factor as well as plasma IL-6 were significantly lower in the animals administered VPA within 3 h ($P < 0.05$) but not when administered later (4, 6, 9 h). There was no difference in the BAL *E coli* colony-forming units, macrophage, or neutrophil numbers at any time point. Survival improved only when VPA was administered within 3 h.

Conclusions: A narrow therapeutic window exists in this murine model of gram-negative pneumonia-induced acute lung injury and likely explains the lack of response in studies with late administration of anti-inflammatory therapies in clinical studies.

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Background

Acute lung injury and respiratory distress syndrome (ARDS) describes a spectrum of pulmonary condition that manifests clinically with severe respiratory failure.[1] The syndrome develops as the lungs mount an exaggerated immune response to a severe inflammatory stimulus resulting from local or systemic insults. Neutrophils recruited to the lungs damage the pulmonary vascular endothelium and alveolar epithelium, leading to increased permeability across and between cells, intrapulmonary hemorrhage, and pulmonary edema due to disruption of the blood-alveolar barrier.[2] These pathologic events taking place at a microscopic level eventually compromise gas exchange and lead to severe hypoxia and respiratory failure, typically necessitating ventilator support.[3]

This inflammatory condition affects more than 200,000 patients annually in the United States alone[3,4] and is associated with over 3.6 million hospital days[3] and excessive long-term functional disability and health care utilization.[5] The mortality of the syndrome is also very high, exceeding 45%—approaching 60% in the most severe cases[6]—making ARDS more lethal than embolic stroke and acute coronary syndromes.[7,8] Despite recent advances in critical care, treatment for ARDS remains largely supportive,[9-11] and targeted anti-inflammatory therapies have failed to improve clinically relevant outcomes in humans. However, these have been typically administered past the exudative stage of the clinical syndrome or around its zenith,[12-14] leaving little room for meaningful improvement. At the same time, subjects on anti-inflammatory therapies at baseline for different, non–ARDS-related indications appear to develop an ameliorated clinical syndrome, if at all, and have improved outcomes, when compared to counterparts not on long-term anti-inflammatory regimens.[15,16] This observation has raised the question: Does timing of therapy play as an important role in the treatment of ARDS, or perhaps even more so, than the therapy itself? Does a therapeutic time window exist, during which, if targeted anti-inflammatory therapies are administered, the maximum clinical benefit can be derived (Fig. 1)? We have previously demonstrated an ameliorated inflammatory phenotype in a well validated and commonly used murine model of gram-negative pneumonia-induced acute lung injury[17-20] utilizing a broad-spectrum histone deacetylase inhibitor (HDACI), valproic acid (VPA), administered early.[21] HDACI is thought to exert at least part of their potent anti-inflammatory effects by interacting with the toll-like receptor, myeloid differentiation factor 88 (MyD88), interleukin-1 receptor kinase (IRAK1), and NF-kB pathway. Pathogen-associated molecular patterns interface with macrophage plasma membrane toll-like receptors and signal through MyD88 and IRAK1 to stimulate nuclear translocation of NF-kB, subsequently turning on the transcription of proinflammatory cytokines.[22,23] HDACIs are known to decrease MyD88 and IRAK1 protein expression, likely by enhancing their degradation due to heat-shock protein 90 hyperacetylation, thereby preventing NF-kB nuclear translocation and cytokine expression *in vivo*.[24] This represents at least one possible mechanism by which the kB-regulated proteins become underexpressed with HDACIs.

With the current project, we explore whether timing of administration of a previously proven to be effective therapy for ARDS[21] has the same efficacy at improving the animal inflammatory profile and overall survival when administered at varied time intervals.

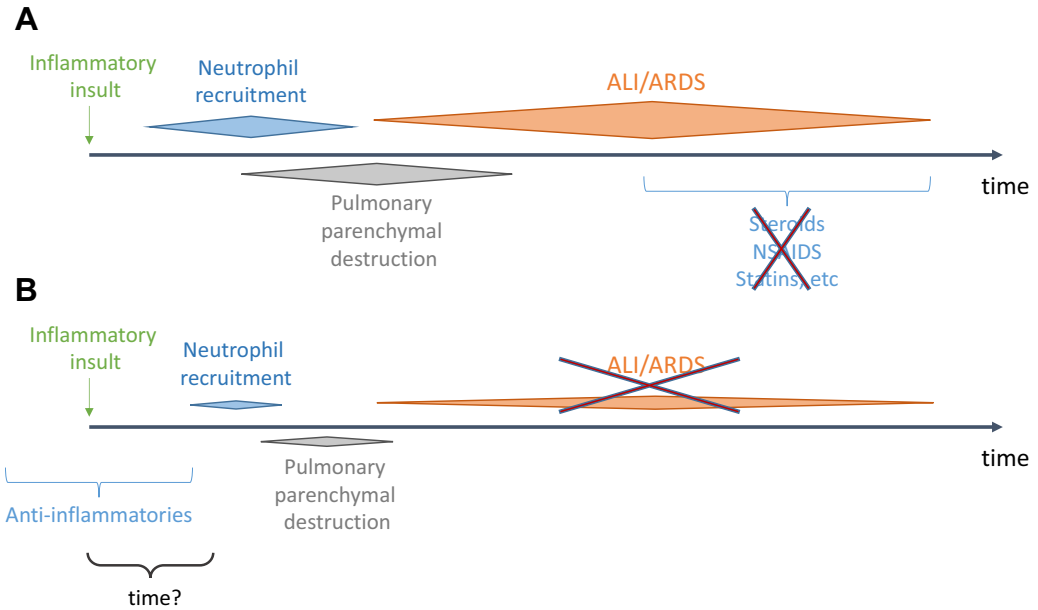

Fig. 1 – Proposed mechanism of effect of timing of administration of anti-inflammatory agents. (A) Anti-inflammatory therapies are of no clinical benefit when administered at the peak of the ARDS syndrome. (B) Patients on chronic anti-inflammatory therapies for nonpulmonary indications appear to develop a much more benign, if at all, clinical syndrome. ALI = acute lung injury. (Color version of figure is available online.)