Montelukast as a Treatment of Acute Lung Injury in Sepsis

Yasin Abul¹, Emel Eryuksel², Sait Karakurt³, Turgay Celikel³ and Berrin Ceyhan³

Acute lung injury is a syndrome including acute and persistent lung inflammation with augmented vascular permeability (1). Sepsis is the most common reason for acute lung injury (2,3). The overall mortality rate of acute lung injury has been reported as 25 – 58%, although recent advances in the management of sepsis have been revealed (4,5). Many studies have pointed out the role of anti-inflammatory treatments of sepsis and sepsis-induced acute lung injury. But anti-inflammatory treatments such as N-acetylcysteine and TNF-alpha blockers have still limited value in the treatment of sepsis-induced lung injury. Sepsis and its effect on lung tissue is a kind of inflammatory storm and it is therefore not easy to control all steps in this inflammatory pathway. On the other hand, the leukotriene receptor antagonist, montelukast, has been shown to ameliorate sepsis induced hepatic and intestinal injury including oxidative stress in rats (6). Montelukast has also been used as an effective agent to decrease fibrosis and oxidative stress in lungs in some animal studies (7,8). Acute lung injury due to sepsis is related to some mediators and cytokines, including fibroblastic growth factor and tumor necrosis factor (TNF-alpha), both of which are released in the inflammatory process of acute lung injury and oxidative stress (9,10). Given the multiple lines of evidence that have emerged to support a central role of leukotrienes, we hypothesize that leukotriene receptor antagonist treatment, particularly with montelukast, may reduce the fibrotic phase of acute lung injury due to sepsis. We believe that if our hypothesis is correct, a new perspective will be opened for the medical management of sepsis-induced acute lung injury.

*Correspondence: abulyasin@yahoo.com
Received: 2009/10/12; Accepted: 2010/02/10; Posted online: 2010/04/30

© 2010 Yasin Abul. This is an Open Access article distributed by Hypothesis under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Introduction

**Sepsis is a severe infection** complicated by systemic inflammation and extensive tissue injury (11). It has been shown that this tissue injury may cause sequential organ failure activated by inflammatory mediators (12,13). Acute lung injury is one of the most important mortality and morbidity factors in sepsis.

Treatment modalities such as starting early intravenous antibiotics, initial fluid resuscitation with a goal directed at the prevention of hypoperfusion, intensive insulin treatment for glucose control, low tidal volume ventilation, or the use of activated protein-C have all been shown to lower the chance of mortality (14). Since inflammation and inflammatory mediators in sepsis-induced acute lung injury play a crucial role in the pathophysiology of sepsis, anti-inflammatory treatment has become a prominent measure (15).

**What are Montelukast and Leukotrienes?**

Leukotrienes are end products of arachidonic acid metabolism and have a role in inflammation by stimulating microvascular permeability and the chemotaxis of leukocytes (16,17). Leukotrienes also function in immunologic responses, apoptosis and cellular proliferation. Furthermore, they have been found to increase chemotaxis of fibroblasts (17,18).

Leukotrienes activate the NADPH oxidase enzyme, causing neutrophilic production of free radicals known to play a role in fibrogenesis (19). Montelukast is a leukotriene receptor antagonist widely used in the treatment of asthma and allergic rhinitis. Interestingly, a number of recent animal studies have shown that montelukast has an anti-inflammatory effect on some sepsis-induced organ diseases, chiefly of liver and intestine (6). However, montelukast has not been used for the treatment of sepsis-induced lung injury. We theorise that, through the NADPH oxidase pathway or chemotaxis of fibroblasts, montelukast may be used to inhibit inflammatory and fibrotic phase in sepsis-induced acute lung injury. Montelukast may also prevent proliferative effect of leukotrienes on inflammatory cells. In addition, montelukast may decrease chemotaxis of fibroblasts. By way of all these mechanisms, montelukast may be a potential candidate for the treatment of sepsis-induced lung injury.

**Leukotrienes and Fibrosis**

Though best known for their role in inflammation, leukotrienes, particularly LTB4, can stimulate fibroblasts and have a chemotactic role for fibroblasts in lung tissue (20,21). They induce fibroblastic proliferation and myelofibroblastic transformation of fibroblasts in the lung. Some leukotrienes, principally the cysteinyltype, are also known to activate NADPH oxidase causing oxygen-free radical production in neutrophils (22,23). These free radicals and leukotriene-induced inflammatory mediators, including fibroblast growth factor and tumor necrosis factor (TNF-alpha), are co-factors for fibrinogenesis in the lung (24).

**Fibrosis has been reported as a poor prognostic factor in acute lung injury**

However, montelukast has been shown to be an effective agent for decreasing fibrosis in some animal studies, especially in the treatment of fibrosis of interstitial lung diseases (8,24). Similar mechanisms regarding the formation of fibrosis are seen in sepsis-induced lung injury. It is known that there is a fibrotic phase in sepsis-induced lung injury that is pathophysiologically similar to fibrotic phase of interstitial lung disease, suggesting anti-inflammatory treatments used in the treatment of fibrotic lung diseases may also be used for the treatment of fibrosis in
Unfortunately, advances in understanding the pathobiology of sepsis-induced lung injury have not yet been translated into effective therapies. We hypothesize that leukotriene receptor antagonist treatment, particularly montelukast therapy, may reduce the fibrotic phase of acute lung injury in sepsis. Clinical trials are of course needed to explore and optimize this potential therapy, first on animals and then on patients with acute lung injury due to sepsis. If our theory is supported, a new perspective will be open for medical management of acute lung injury in sepsis.

References
7 Izumo T, Kondo M, Nagai A. Cysteinyl-leukotriene 1 receptor antagonist attenuates...


30 Meduri GU, Chinn A. Fibroproliferation in late adult respiratory distress syndrome.
Pathophysiology, clinical and laboratory manifestations, and response to corticosteroid rescue treatment. Chest 1994;105(3 Suppl):127S-9S.


