Why Clinical Trials Might Succeed in Acute Pancreatitis when They Failed in Septic Shock

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Sepsis and acute pancreatitis, which bear a significant morbidity and mortality, are two diseases frequently encountered in intensive care units. Twenty percent of patients with acute pancreatitis have a severe form of the disease and 15-20% of them will die [1]. The mortality in septic shock varies from 40 to 60% [2]. Interestingly, both diseases have several features in common: the occurrence of multiple organ dysfunction over time and the involvement of mediators such as cytokines in the pathogenesis of the disease [3, 4, 5]. While numerous therapeutic clinical trials have been carried out in patients suffering from septic shock, only a small number of trials were done in patients with acute pancreatitis. In septic shock, the results of such trials have been disappointing for several reasons, all of which have been emphasized in recent literature. However, such treatments, which failed during septic shock, might be of interest in patients with severe acute pancreatitis. This hypothesis will be the focus of our article.

Clinical Trials in Septic Shock

Many pro-inflammatory mediators have been involved in the physiopathology of sepsis [3]. Tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) are two major mediators of the early host response to bacteria proliferation. In experimental septic shock, concentrations of TNF-α and IL-1 increase, thus promoting the release of IL-6 which is responsible for the acute phase response [6, 7, 8]. IL-8, IL-12 and products released by activated leukocytes such as O_2-derived free radicals and platelet-activating factor (PAF) are also involved at the beginning of the systemic inflammation. A concomitant anti-inflammatory response is also evidenced by the increased synthesis of IL-10, soluble TNF-α receptors and the IL-1 receptor antagonist (IL-1ra) which counteract the effects of the pro-inflammatory mediators. Interestingly, the survival rate during sepsis is increased when animals are treated either by the inhibition of these pro-inflammatory cytokines or by IL-10, soluble TNF-α receptors and IL-1ra.

Following these promising experimental findings, large clinical trials have been initiated. Early clinical trials demonstrated that the inhibition of pro-inflammatory mediators was able to reduce the mortality of septic patients by 10%. However, many subsequent clinical trials failed to improve the outcome of septic shock and the reasons for such failure are numerous [9, 10, 11, 12]. Most clinical trials were unable to evidence a 10% improvement of the overall mortality in septic patients because they were not large enough [13]. To enroll patients in clinical trials, positive microbiological cultures were not required and only a limited number of patients had positive cultures. The criteria of inclusion did not consider the length of the infection before enrollment nor the anatomic site of the infection. Most of the criteria used in these trials included clinical features which defined the multiple organ dysfunction.

Moreover, although various immuno-modulatory treatments were beneficial in experimental models of sepsis, the extrapolation of these findings to patients might be questionable. Indeed, most experimental models of sepsis used a single injection of endotoxin and this experimental model greatly differs from clinical sepsis. Moreover, treatments have been injected in animals before the septic challenge. Cecal ligation and puncture which create polymicrobial peritonitis mimicking a perforated appendix and diverticulitis observed in human sepsis might be a more appropriate model. In this experimental model of sepsis, cytokine blockade has, for the most part, been unsuccessful. Moreover, animals are healthy and do not suffer from underlying diseases as is frequently observed in humans. Another reason for the failure of clinical trials might be that septic patients were heterogeneous with many co-morbidities associated with sepsis [14]. Consequently, the mediators of inflammation greatly differ from one patient to another. For example, most of the patients included in anti-TNF-α trials had normal plasma concentrations of TNF-α when the treatment began. In contrast, anti-TNF-α antibodies are effective in homogeneous groups of patients suffering from well-characterized chronic pathologies such as Crohn's disease [15] or rheumatoid arthritis [16]. Additionally, the onset of sepsis is difficult to determine precisely. Thus, it is difficult to treat each patient at the same time-point of the disease. Finally, the classic endpoint of all clinical trials is the 28-day overall mortality [2, 3]. Due to the various events which occur in intensive care units and the severe underlying diseases of these patients, a single therapy might be insufficient to significantly modify the outcome of the disease.

Similarities between Sepsis and Acute Pancreatitis

Acute pancreatitis is also a severe inflammatory disease frequently encountered in intensive care units [1] (Table 1). It is diagnosed mainly by acute abdominal pain associated with a concomitant rise of serum amylase and lipase concentrations. Gallstone migration into the common bile duct and alcohol abuse account for most of the etiologies of the disease. Usually the injury is mild, but 20% of the patients have a severe injury and, among them, 15 to 25% will die. In recent years, treatment of these patients has greatly improved following a better understanding of the pathophysiology of the disease [17, 18]. This pathophysiology includes the activation and release of pancreatic enzymes in the interstitium, the autodigestion of the pancreas and a multiple organ dysfunction following their release into the systemic circulation. In 1988, Rinderknecht [19] first hypothesized that cytokines may also play an important role and suggested that inappropriate activation of the immune system might increase the severity of the local disease and the systemic complications. Over the past few years, significant evidence has been accumulated indicating that the synthesis and release of pro-inflammatory cytokines and chemokines were responsible for the local injury and the systemic dispersion of the inflammation [20,

Table 1. Similarities between septic shock and acute pancreatitis.

	Septic shock	Acute pancreatitis
Severe inflammatory disease	Yes	Yes
Pro-inflammatory mediators involved in the disease	Yes	Yes
Anti-inflammatory response	Yes	Yes
Multiple organ dysfunction in the evolution of the disease	Yes	Yes
Benefit of immunomodulatory treatments in experimental models	Yes	Yes

21, 22]. Thus, inflammatory mediators produced within the gland increase the pancreatic injury and spread to distant organs, transforming a local inflammation into a severe systemic disease. Interestingly, the mediators involved in this systemic inflammation are similar to those encountered during sepsis. Moreover, an anti-inflammatory response is also initiated which includes the synthesis of IL-10 and IL1ra [23, 24, 25].

Because it is important to predict the severity of the disease as early as possible in order to optimize the therapy and to prevent organ dysfunction and local complications, several scores such as Ranson [26], Glasgow [27] and the Acute Physiology And Chronic Health Evaluation (APACHE II) [28] scores have been used. Recently, new serum markers have emerged and their ability to provide additional information on the severity of the disease has been evaluated [29]. Interestingly, because the serum concentration of some of these markers is correlated to the severity of the disease and because they are detected before the occurrence of multiple organ dysfunction, it is then conceivable that the therapeutic antagonism of these mediators might prevent or attenuate the severity of the multiple organ dysfunction, and consequently the outcome of the disease.

Thus, common mediators are involved in the pathogenesis of both diseases and interestingly most of the reasons why clinical trials failed in septic shock can be avoided in acute pancreatitis.

Why Clinical Trials Might Succeed in Acute Pancreatitis when They Failed in Septic Shock

Criteria for the diagnosis and the classification of the severity of acute pancreatitis are better defined than those of sepsis (Table 2). The routine availability of early markers of severity, such as trypsinogen activated peptide [30, 31], IL-6 [32, 33, 34], and IL-8 [35, 36] should improve the selection of severe patients before the development of multiple organ dysfunction. Consequently, the early administration of antagonists targeting these factors should improve the outcome of the disease and prevent the development of multiple organ dysfunction. Patients included in clinical trials are more homogeneous in acute pancreatitis than in sepsis. Underlying diseases are less common than in sepsis. Additionally, the cause of acute pancreatitis moderately influences the evolution of the disease [37].

During acute pancreatitis, the time of onset is easy to determine because the first abdominal pain is usually well-described by the patient. For that reason, it is possible to standardize the timing of treatment administration. Provided that the patient is admitted soon after the onset of abdominal pain, the therapeutic window is between 24 and 48 hours [22].

The early clinical trials for severe pancreatitis have been disappointing. Administration of proteolytic enzyme inhibitors, steroids and inhibitors of pancreatic exocrine secretion did

Table 2. Why clinical trials might succeed in acute pancreatitis when they failed in septic shock.

	Septic shock	Acute pancreatitis
Precise diagnostic of the disease	No	Yes
Specific biological criteria for the diagnosis	No	Yes
Onset of the disease easy to determine	No	Yes[*]
Heterogenous population	Yes	No
Frequent underlying diseases	Yes	No
Early treatment at the onset of the disease	No	Yes

* Abdominal pain

not alter the course of severe pancreatitis [38, 39, 40]. In recent years, the only trials targeting an inflammatory mediator in acute pancreatitis used the inhibitor of PAF receptor, lexipafant [41, 42, 43]. PAF is a low molecular weight phospholipid which acts via specific cell surface receptors on platelets, leukocytes and endothelial cells. Normal acini synthesize PAF but, during acute pancreatitis, pancreatic and pulmonary tissue as well as blood concentrations rise, indicating that PAF is a key mediator of the systemic inflammatory syndrome. When patients with severe acute pancreatitis were treated with lexipafant at admission for up to 3 [41] or 7 [42] days, the severity score for organ dysfunction was lower in the treated group than in the group of patients treated with saline. However, a recent study showed the absence of the efficacy of the inhibition of PAF in improving the severity of the disease more definitely [43]. Interestingly, when severe septic patients were treated with lexipafant for up to 3 or 7 days, the 28-day mortality was similar in the treated and control groups [44].

Nevertheless, other agents, such as PAF acetylhydrolase, might be tested during acute pancreatitis. This enzyme which degrades PAF might represent another way to inactivate PAF [45]. Its efficacy has been proven in opossum, and clinical trials have started in the USA. The development of additional immunomodulatory clinical trials might also be helpful. Thus, similarly to clinical trials in sepsis shock [46, 47], antibodies to TNF-α, soluble TNF-α receptors, IL1-ra, and soluble IL-1 receptors might be tested. IL-10, which reduces the incidence of acute pancreatitis after therapeutic endoscopic retrograde cholangiopancreatography might be another candidate [48].

Conclusion

In conclusion, although anti-inflammatory drugs have failed to improve the outcome in septic shock, a reassessment of the potential benefits of such treatments in acute pancreatitis might be interesting. Considering the lessons learned from the clinical trials in septic shock and the reasons for which these trials failed, patients suffering from acute pancreatitis might benefit from these anti-inflammatory treatments.

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