JOP. J Pancreas (Online) 2004; 5(3):115-121.

EDITORIAL

Immune-Manipulation of the Inflammatory Response in Acute Pancreatitis. What Can Be Expected?

Raffaele Pezzilli, Rosa Ceciliato, Bhajat Barakat, Roberto Corinaldesi

Department of Internal Medicine, Sant'Orsola-Malpighi Hospital. Bologna, Italy

Summary

Severe acute pancreatitis still has a high mortality rate and multiple organ failure is considered to be a severe complication of the disease. Activated polymorphonuclear leukocytes have an important role in the development of multiple organ failure which may result from acute pancreatitis and they are an important pathogenetic factor in the severity of this disease. Therefore, a logical therapeutic approach is to limit the organ damage by selective suppression of inflammatory mediators involved in the systemic inflammatory response syndrome and protect against systemic complication. In this paper, we review the recent literature data on the possible manipulation of the immune response in acute pancreatitis.

Severe acute pancreatitis still has a high mortality rate of about 14-35% [1, 2, 3, 4, 5, 6,7, 8, 9], and multiple organ failure (MOF) is considered to be a severe complication of the disease. The mortality rate was higher in patients having both organ failure and necrotizing pancreatitis as compared to those having only necrotizing pancreatitis without organ failure, independent of whether the necrosis was sterile or infected [10, 11, 12]. Activated polymorphonuclear leukocytes have an important role in the development of MOF which may result from acute pancreatitis and they are an important pathogenetic factor in the severity of this disease. The release of inflammatory mediators from activated polymorphonuclear leukocytes plays a predominant role in the development of complications [13]. MOF in acute pancreatitis is similar to that in sepsis, trauma and burns, and is characterized by a systemic inflammatory response syndrome (SIRS) [13, 14]. Therefore, a logical therapeutic approach is to limit the organ damage by selective suppression of inflammatory mediators involved in the SIRS and protect against systemic complication.

At present, there are several possibilities to modulate the inflammatory response: 1) manipulate the cytokine network, 2) suppress the inflammatory response, 3) active immunization, 4) the induction of tolerance, 5) the administration of immunoglobulin and 6) gene therapy. In acute pancreatitis, only the first two points have been explored until now, experimentally as well as in clinical practice.

Before introducing the topic of this paper, we would like to emphasize that, in acute pancreatitis, the therapeutic window for intervention is an important point and it has been well described by Norman [15]; the useful time elapsed from the onset of pain to the first manifestation of organ dysfunction is about 48-72 hours. From this assumption we only have a short time interval during which specific therapy should be administered; thus, we need to rapidly diagnose and assess the severity of acute pancreatitis. From a practical point of view, since the morphological

appearance of necrosis on imaging technique requires about 48 hours [16], other diagnostic modalities have been proposed, such as the simultaneous serum assays of lipase and interleukin-6 (IL-6) for the early diagnosis and prognosis of acute pancreatitis [17]. Furthermore, the inflammatory response is unrelated to the etiology of acute pancreatitis [18] and, most importantly, the cytokine gene polymorphisms seem to have no role in determining the disease severity [19].

What do we ask of immune-modulation therapy? We ask the prevention of: 1) progression from edematous to necrotizing pancreatitis, 2) SIRS, 3) organ dysfunction and 4) infection of necrosis.

Regarding the progression from edematous to necrotizing pancreatitis, a specific role is played by the NF-kappaB, a transcriptional activator associated with immediate early gene activation. NF-kappaB activation can be stimulated by multiple mediators even if the exact mechanism of activation is not entirely known. In addition to the production of acute phase proteins and adhesion molecules, NF-kappaB has been involved in stimulating the production of several inflammatory cytokines, including tumor necrosis factor-alpha (TNF-alpha) [20, 21]. In this respect, amobarbital is able to block NF-kappaB activation when given 3 hours before induction of pancreatitis and has been demonstrated to be capable of preventing the activation of NF-kappaB and the overexpression of TNF-alpha gene with a significantly decreased severity of pancreatitis in rats [22]. It has also been demonstrated that raxofelast, an inhibitor of lipid peroxidation, reduces acinar cell damage in rats via inhibition of pancreatic NF-kappaB activation, TNF-alpha mRNA levels and tissue content of mature protein in the pancreas [23]. However, due to very early activation of NF-kappaB, it does not seem possible to transpose these results to humans. At present, the only possible route to follow seems that of blocking the effects of TNF-alpha. Hughes *et al*. [24] showed that administration of polyclonal anti-TNF-alpha 15 minutes before the induction of necrotizing acute pancreatitis in rats was able to improve biochemical and histologic parameters as well as overall survival. At present, we have some possibilities of pharmacologically blocking the action of TNF-alpha: Abciximab, a chimaeric Fab fragment that binds to the beta3 integrin of the GPIIb/IIIa and alphavbeta3 receptors on human platelets, approved in the US and Europe for use in percutaneous coronary intervention [25]; infliximab, a chimeric IgG1 antibody specific for human TNF-alpha, approved in the US and Europe for the acute treatment of the signs and symptoms of Crohn's disease and for the chronic treatment of rheumatoid arthritis [25] and etanercept, a fusion protein, composed of the Fc portion of IgG1 and the extracellular domain of the TNF receptor [26]. A recent study has demonstrated that infliximab ameliorated both parenchymal and fatty tissue necrosis of the rat pancreas; it also alleviated alveolar edema and acute respiratory distress syndrome such as pulmonary complications, but the difference was not significant [27]. The main problem in all these studies is that the drugs were administered before or simultaneously with the induction of acute pancreatitis and this is obviously not possible in humans.

Regarding the prevention of SIRS and organ dysfunction several studies have been published where various substances able to block or inactivate the cytokine cascade have been utilized. An interesting aspect is the inhibition of the interleukin 1beta-converting enzyme (ICE); cytokines activated by the ICE play an instrumental role in the course of acute pancreatitis and recent studies have shown that the pharmacological or genetic blockade of the ICE significantly ameliorates the overall severity of and the death rate in various inflammatory disorders [28, 29, 30]. On this basis, Paszkowski *et al*. [31] have shown that an inhibitor of the ICE administered 6 or 12 hours after the induction of severe acute pancreatitis determined a significant reduction of acinar cell necrosis in both treated groups and there was a substantial reduction of neutrophil-mediated tissue injury in the pancreas and lung which contributes to the beneficial effects of this

approach. This approach is also very important from a clinical point of view because the drug was administered after the induction of acute pancreatitis and ICE inhibition was still effective after a therapeutic window of 12 hours after the onset of the acute illness. To decrease the failure of distant organs, a monoclonal anti-IL-8 antibody (WS-4) has also been utilized in a rabbit model of severe acute pancreatitis [32]. Pre-treatment of animals with WS-4 resulted in significant down regulation of serum IL-8 and TNF-alpha from three to six hours after the induction of acute pancreatitis, a significant reduction in the CD11b and CD18 positive cells and the amount of interstitial neutrophil infiltration in the lungs. However, WS-4 did not alter the amount of pancreatic necrosis and the serum concentrations of amylase, lipase, calcium, and glucose. A hypothesis that can be drawn from this study is that a combination of substances modulating the immune system is necessary to reduce local complications and distant organ failure in acute pancreatitis.

The last point, but not the least important, is the possibility of preventing the infection of necrosis. At present, we have the possibility of using antibiotic prophylaxis in patients with extended pancreatic necrosis to decrease the risk of infection [33]. However, also in this case, cytokine therapy may play a role by using IL-2 [34]. In fact, in mice treated with recombinant human IL-2 at a dosage of 15,000 U of recombinant human IL-2 given intraperitoneally and then challenged with lipopolysaccharide, 5-day survival after septic challenge was significantly greater in the IL-2–treated animals (62.5%) than in the vehicle-treated controls (0% survival; P=0.012).

Caution should be used regarding the experimental studies; the utility of such experimental models might be limited and full extrapolation of experimental data from animals to humans must be done with caution. One example is that of therapy with IL-10; Zou *et al*. [35] have demonstrated that, after hIL-10 gene therapy, hIL-10 levels in the pancreas, liver, and lungs increased significantly and serum amylase, tissue TNF-alpha, and histological changes in pancreas, liver, and lungs decreased markedly. Mortality was also significantly reduced in the hIL-10 gene therapy group, in which 70% of rats survived in the 7 day observation, while only 10% survived in untreated groups ($P<0.05$). In contrast, a recent study from a Spanish group in human severe acute pancreatitis, was not able to confirm experimental studies [36]. These authors found that, even in a small patient population, there were no significant differences between IL-10 and placebo groups regarding the days of hospital stay, CT scan score, organ failure score and local complications; furthermore, 50% of the patients in the IL-10 group and 43% in the placebo group developed organ failure.

Another possibility for immune-manipulation therapy is to suppress the inflammatory response. Several drugs such as FK506 [37], OKT3 [37] and corticosteroids [38] have been tested with success in severe acute pancreatitis but the results are limited only to these animal studies. In particular, single therapeutic doses of FK506 and OKT3 reduced the early severity of pancreatitis, pulmonary damage, and hemoconcentration in mice and may therefore be effective in preventing the early complications of pancreatitis [37], whereas hydrocortisone administered intravenously 10 minutes after the induction of acute pancreatitis was able to reduce the early systemic inflammatory response syndrome associated with severe acute pancreatitis and significantly decreased the mortality (P=0.001) [38]. Also in this case, these findings have not been verified in clinical practice.

At present, the question is whether or not we have drugs able to manipulate the inflammatory response and available to our patients in clinical practice; the answer is "yes", but, also in this case, the results should be taken with caution.

The platelet activating factor (PAF), together with other proinflammatory cytokines such as IL-1beta, IL-6, IL-8, TNF-alpha and the anti-inflammatory cytokines IL-2 and IL-10, is involved in the pathogenesis of SIRS in acute

pancreatitis [39]; PAF increases vascular permeability, induces leucocyte infiltration, edema and tissue injury, and has a negative inotropic effect [40]. PAF antagonists have ameliorated acute pancreatitis in experimental models of acute pancreatitis [39, 40, 41, 42, 43], and lexipafant is one of the most powerful PAF antagonists developed so far [44]. Two phase II randomized trials involving a total of 133 patients with acute pancreatitis showed significant improvement in organ failure scores [45, 46]. Recently, a randomized, double blind, placebo controlled, multicenter trial of lexipafant involving 290 patients with an APACHE II score greater than 6 was carried out [47]. The aim of this study was to evaluate the reduction of complications from 40 to 24%; the secondary end point was the reduction of organ failure, markers of the inflammatory response and the mortality rate. Even if the high incidence of organ failure within 72 hours of the onset of symptoms undermined the primary hypothesis and lexipafant had no effect on new organ failure during treatment determining that antagonism of PAF activity on its own is not sufficient to ameliorate SIRS in severe acute pancreatitis, some positive aspects should be pointed out: in the lexipafant group, there was a significant reduction of the incidence of pseudocysts, systemic sepsis and deaths in patients treated within the first 48 hours from the onset of the symptoms. Thus, it is reasonable that, for anti-cytokine therapy, the therapeutic window is a crucial point to test its efficacy and, secondarily, other and associated therapeutic approaches should be put in action together with the immune-therapy for the appropriate treatment of acute pancreatitis.

Another possibility of reducing the inflammatory response in acute pancreatitis comes from the use of gabexate mesilate. Gabexate mesilate is a potent synthetic serine protease inhibitor [48] and it has been demonstrated to significantly decrease TAP levels in both lymph and blood, and to reduce pancreatic injury [49]. In a human study involving 24 patients with severe acute pancreatitis [50], gabexate was able to significantly reduce the inflammatory response evaluated by serum C-reactive protein levels (CRP).

The last possibility of reducing the inflammatory response in humans with severe acute pancreatitis is the use of total enteral nutrition. Failure of the intestinal barrier, together with bacterial overgrowth due to motility changes and immunosuppression, constitute the pathways of continuous pancreatic contamination from bacterial translocation in patients with severe acute pancreatitis [51]. One of the first studies on this topic [52] demonstrated that total enteral nutrition was able to moderate the acute phase response evaluated by serum C-reactive protein determination, serum IgM antiendotoxin antibodies and total antioxidant capacity, as well as to improve disease severity and clinical outcome despite unchanged pancreatic injury on computed tomography scan. Most importantly, the immediate institution of nutritional support in the form of total enteral nutrition is as safe in predicted severe acute pancreatitis as total parenteral nutrition [53]. Although the CRP concentrations in the two groups were not significantly different on any of the measurement days, the values of CRP recorded in the total enteral nutrition group are lower than those expected in patients with predicted severe acute pancreatitis. More information on the immune manipulation using enteral nutrition may be obtained by further studies who investigate the use of different enteral preparations as well as the association of enteral nutrition with probiotics [54].

In conclusion, the immune manipulation of the inflammatory response represents the dawn of a new day in the treatment of severe acute pancreatitis; we are waiting for a new day, but we have to keep in mind that modulation of the immune response is only a part of the multimodal treatment of acute pancreatitis involving multidisciplinary specialists such as internists, gastroenterologists, surgeons, endoscopists and intensivists. We also must be aware of several autoimmune phenomena in patients

treated with cytokine and anticytokine therapies, such as the development of antinuclear antibodies, development of anti-cardiolipin antibodies, systemic lupus erythematosus, neurological signs and symptoms associated with demyelinating lesions of the central nervous system, development of antithyroid antibodies, thyroid dysfunction, arthritis, myositis, systemic sclerosis, pemphigus vulgaris, vitiligo and so on [55].

Keywords Animal Experimentation; Cytokines; Human Experimentation; Pancreatitis, Acute Necrotizing; Pharmaceutical Preparations; Therapeutics

Abbreviations CRP: C-reactive protein; ICE: interleukin 1beta converting enzyme; and IL: interleukin; MOF: multiple organ failure; PAF: platelet activating factor; SIRS: systemic inflammatory response syndrome; TNF-alpha: tumor necrosis factor-alpha

Correspondence
Raffaele Pezzilli
Dipartimento di Medicina Interna
Ospedale Sant'Orsola-Malpighi
Via G. Massarenti, 9
40138 Bologna
Italy
Phone: +39-051.636.4148
Fax: +39-051.549.653
E-mail: pezzilli@orsola-malpighi.med.unibo.it

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