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Invited review

Immune modulation of pancreatic diseases: Any future for clinical applications?

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INTRODUCTION

Regardless of whether the initiating event is gallstones, alcohol or any other less common cause, acute pancreatitis (AP) starts with the unappropriate activation of intracellular digestive enzymes that leads to the self digestion of parts of this organ. This is usually followed by a local inflammatory reaction. In the majority of the cases, AP is a self limiting disease that resolves spontaneously without any sequel.[1] In other cases, the initial inflammatory reaction may be more severe and leads to the development of local necrosis. This occurs after monomacrophagic and polymorphonuclear cells have invaded the pancreas, a feature observed within a few hours after the initial enzymes activation.[2]

A major particularity of AP, among other non infectious diseases of the gastrointestinal tract, is its propensity, when it becomes severe, to disclose an amplification of the localized inflammatory process through a systemic inflammatory response. This leads to the development of multiple organ disturbances which are mainly responsible for the morbidity and mortality related to this disease.

The other factor which promotes the development of systemic inflammatory response is the possible infection of local necrosis of the pancreas, one of the major clinical feature affecting the morbidity of the disease.[3]

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Most of the AP research has centered on identifying the possible ways of modulation of the early necrotic process, of the infection of pancreatic necrosis and, most importantly, on the better knowledge of the inducers of the systemic disease as well as the possibilities to modulate the unappropriate pro-inflammatory systemic response.

MODULATION OF THE EARLY PHASE OF AP: ANTIPROTEASES, SOMATOSTATIN

Experimental studies have shown that blocade of trypsin, elastase and phospholipase with antiproteases administered per os or intraveinously is effective in the treatment of acute experimental pancreatitis.[4] However, their clinical application is limited by the fact that they have to be given very early in the course of the disease and that, after the onset of AP, they are often given too late to exert their potential control of the initial intracellular phase of pancreatitis. They have been however shown to be useful in the single model of human clinical pancreatitis in which a prophylactic treatment can be administered, namely post-ERCP pancreatitis.[5]

The same comments can be given about somatostatin and octreotide, two compounds which decrease pancreatic enzymes secretion but which have a limited usefulness when pancreatic necrosis has already developed. In the same line that protease inhibitors, they have only been shown as potentially useful for the prevention of pancreatic injury after ERCP[6] or when given for a short period, rapidly after the onset of symptoms.

PREVENTION OF PANCREATIC NECROSIS DEVELOPMENT AND OF SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS): THE ROLE OF CYTOKINES (Figure 1)

Over the last 10 years, with a better characterization of cytokines as systemic mediators of inflammation and a better knowledge of their relationship with other compounds like bradykinine, complement and nitric oxyde, as well as with the identification of an endogeneous pro and anti-inflammatory response, the development of systemic complications during severe pancreatitis has become better understood. Moreover, it now clearly appears that during the few hours after the development of AP, in the absence of any histological alteration, a systemic production of cytokines is already present at the level of other organs like the lung or the liver.[7,8] This multisystemic production of cytokines includes proinflammatory cytokines such as interleukin 1(IL-1), tumor necrosis factor (TNF) and platelet activating factor (PAF) but also the endogenous production of anti-inflammatory mediators of which IL-10 is probably the most important. It is when the homeostatic balance between pro and anti-inflammatory cytokines production is overwhelmed than multiple organ failure starts to develop.

Many experimental studies have now been published, showing in various pancreatitis models that the antagonism of IL-1, TNF or PAF early in the course of pancreatitis will decrease its severity and eventual mortality. In the same line, the exogenous administration of IL-10 has a similar effect on the prevention of pancreatic necrosis and of systemic consequences of the disease.

However, in most of these models, anti-inflammatory cytokines or inhibitors of pro-inflammatory cytokines are given before or very early after the induction of pancreatitis and their activity disappears when they are given later when the disease is already prominent.

Is anticytokine therapy for AP a clinical possibility ?

As proinflammatory cytokines production starts early, within a few hours after the onset of pancreatitis, they should be modulated also very early in the course of pancreatitis. The major limitation of anticytokine therapy is that it has to be given within a relatively limited therapeutic window, most probably located between 6 and 36 hours after the onset of clinical symptoms (Figure 2).

Although only a few patients, presenting shortly after the onset of pain, will exhibit organ dysfonction, it is clear at that time, that anticytokine therapy should be proposed to prevent distant organ dysfonction in a significant larger number of individuals. Therefore, anticytokine therapy should be given early and on the basis of biological or clinical factor which are potential predictors of pancreatic severity. In this line, new biological factors are clearly needed, of which interleukin 6 (IL-6) is probably the most sensitive. The previous clinicobiological scores or the classification of severity based on imaging, have become old-fashioned due to their lack of sensitivity at the very early phase of pancreatitis.

Up to now, the therapeutic window for inflammatory mediator antagonism has been supported in the results of phase III clinical trials with lexipafant (PAF antago-

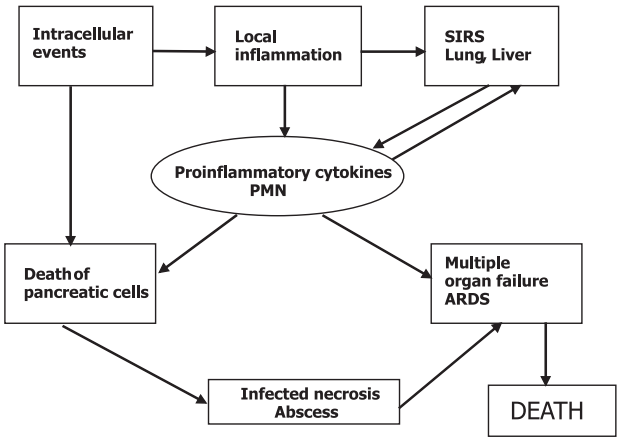

Figure 1. The pathophysiological pathways of AP and associated systemic complications.

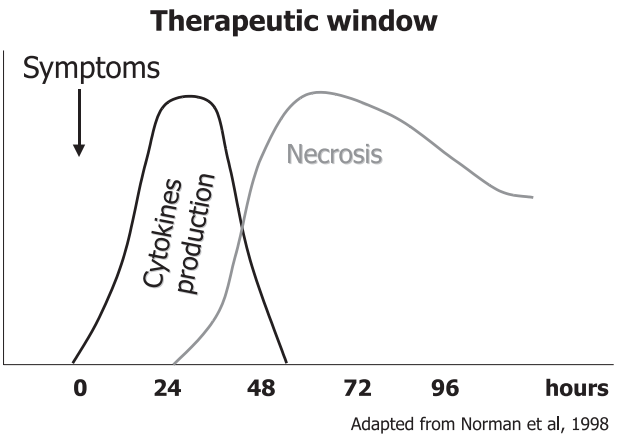

Figure 2. Time course of pancreatitis progression demonstrating a therapeutic window for inflammatory mediator antagonism.

nist) in severe acute pancreatitis, which was shown to be most beneficial when given within 24 hours of pain onset.[9,10] This is also the reason why the multicenter trial of PAF antagonists used for the prevention of organ failure in predicted severe acute pancreatitis[11] was somewhat disappointing. It is indeed very difficult to include a patient in such a double blind randomized trial within 48 hours after pain onset. Moreover, Lexipafant had the drawback of being given in continuous perfusion which makes its administration more difficult. Interleukin 10 can be given as a single dose since its half-life in the blood lasts more than 24 hours. This potent anti-inflammatory cytokine has been tested in the prevention of post-endoscopic retrograde cholangiopancreato-graphy pancreatitis which is the closest human correlate of experimental animal pancreatitis. Indeed, it is known than when selecting high risk patients (namely those who need pancreatic endoscopy and do not have advanced chronic pancreatitis), the risk of developing pancreatitis after ERCP is between 10 and 20%. In a double blind randomized trial, it has been shown that a single intraveinous dose of IL-10, given 30 minutes before the start of the procedure in patients at high risk of developing post-ERCP pancreatitis, independently reduces the incidence of post-therapeutic ERCP pancreatitis.[12] A multicentric trial is currently ongoing in order to determine if this treatment can reduce the incidence of severe acute pancreatitis which represents the major complication of ERCP.

In conclusion, recent development in understanding the pathophysiology of severe acute pancreatitis have let to the design of possible new treatments able to modify the early course of pancreatitis, within a very short therapeutic window. In this context, anticytokines therapy seem to be promising although their routine clinical application is not yet proposed. Post-ERCP pancreatitis is the most easy model to be studied but future applications could be advocated in the setting of very early treatment of acute pancreatitis, maybe given at the emergency room, in the setting of a simple protocol.

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