Lesson from Acute Experimental Pancreatitis: Multidrug Strategies Is Effective than Single-Target Therapy

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Current strategy of treatment in acute pancreatitis is mainly based on supportive measures, adequate analgesia, elimination (if possible) of any underlying cause, and prevention of complications. Many "specific" therapies able to interrupt one key step in the pathogenesis of local and systemic injury have been proposed but no single therapy has been shown to significantly decrease acute pancreatitis mortality. Over the last few years, lessons from experimental animal models helped us to better understand many important pathways involved in the pathogenesis of necrotizing acute pancreatitis and associated systemic complications. In this setting, multiple mediators of the inflammatory cascade, including oxygen-free radicals, vasoactive mediators, cytokines, leukocyte and endothelial activation, and pancreatic ischemia have been identified. In experimental studies (mainly in animal models but also in humans), several drugs that specifically inhibit each of those pathogenetic steps (e.g., protease inhibitors, oxygen-free radical scavengers, cytokine antagonists, nitric oxide (NO) agonists, and inhibitors of adhesion molecules) attenuated biochemical and histological changes; however, neither the inhibition of pancreatic auto-digestion nor the inhibition of any other single pathogenetic factor has decreased mortality in cases of severe acute pancreatitis.

Keeping these data in mind, the basic question could be the following: is it possible that the combination of multiple drugs able to simultaneously counteract the most important pathogenetic mechanisms could result more effective than all single-agent monotherapies? This intriguing question was recently addressed in a noteworthy study by a group of researchers from the Departments of Experimental and General Surgery of University of Heidelberg and Rostock, Germany [1]. The aim of their study was to evaluate a multidrug ''cocktail'' regimen that combined drugs directed at several acute pancreatitis specific pathogenetic events. The effects on pancreatic and systemic injury , as well as on survival, were assessed in a rat model of acute necrotizing pancreatitis (retrograde bile injection combined with intravenous cerulein). After a therapy-free interval of 6 hours, 10 treatment regimens were evaluated: multidrug regimen A, which contained 5 drugs dissolved in dextran (protease inhibitor gabexate mesilate, plus oxygen-free radical scavengers, plus NO-donor L-arginine, plus a platelet-activating factor antagonist, and plus antibodies against intracellular adhesion molecule-1 (ICAM-1)) , was compared to multidrug regimen B, which contained 3 drugs (acetylcysteine, L-arginine, and anti-ICAM-1 in dextran), monotherapies of each of the drugs, and standard intravascular volume replacement. In this complex experimental setting both multidrug regimens significantly reduced pancreatic and systemic injury and microcirculatory disturbances compared to any of the monotherapies. Treatment with regimen A decreased 24-hour mortality to 0% and increased long-term survival to 85% (standard therapy: 70% and 15%, respectively). Multidrug regimen B was as effective as regimen A. In addition, the study also revealed that the mortality of severe acute pancreatitis did not further increase when the multidrug approach was used after a therapy-free interval of 12 hours. This event is likely due to the attenuation of systemic inflammatory response, extracellular fluid shifts, and multi-organ failure, all major causes of early death in acute pancreatitis both in animals and humans.

Severe acute pancreatitis is still associated with a high mortality rate of 15-30%, with early mortality still playing a significant role. Data of Werner and co-workers shows for the first time that a combination of drugs that are directed against several different pathways involved in the pathophysiologic events in severe experimental pancreatitis is superior to monotherapies and standard volume therapy, decreasing overall mortality of severe necrotizing pancreatitis. We clearly know that all experimental models and studies have their limitations, but the presented study shows that multidrug approaches are promising treatment options that should be transferred to the clinic. These results need confirmation in a clinical trial with strict evaluation of efficacy, cost-

effectiveness, and toxicity. In my opinion, this experimental study represents a perfect example of what we should expect by a "*from the bench to bedside*"-guided research in pancreatology.

Key words Cell Adhesion Molecules; Cytokines; Free Radical Scavengers; Nitric Oxide; Pancreatitis, Acute Necrotizing; Protease Inhibitors; Therapeutics

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