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# Pharmacologic therapy for acute pancreatitis

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from past clinical studies are likely to offer a great foundation upon which to expand future therapies in acute pancreatitis.

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**Key words:** Acute pancreatitis; Antisecretory; Protease inhibitors; Anti-inflammatory; Anti-oxidants; Systemic inflammatory response syndrome; Organ failure; Mortality

**Core tip:** Currently there are no approved therapies for acute pancreatitis. This review summarizes and discusses pre-clinical and clinical studies in acute pancreatitis and also discusses potential promising therapies.

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## Abstract

While conservative management such as fluid, bowel rest, and antibiotics is the mainstay of current acute pancreatitis management, there is a lot of promise in pharmacologic therapies that target various aspects of the pathogenesis of pancreatitis. Extensive review of preclinical studies, which include assessment of therapies such as anti-secretory agents, protease inhibitors, anti-inflammatory agents, and anti-oxidants are discussed. Many of these studies have shown therapeutic benefit and improved survival in experimental models. Based on available preclinical studies, we discuss potential novel targeted pharmacologic approaches that may offer promise in the treatment of acute pancreatitis. To date a variety of clinical studies have assessed the translational potential of animal model effective experimental therapies and have shown either failure or mixed results in human studies. Despite these discouraging clinical studies, there is a great clinical need and there exist several preclinical effective therapies that await investigation in patients. Better understanding of acute pancreatitis pathophysiology and lessons learned

## INTRODUCTION

In the United States in 2009, over 274000 patients were diagnosed with acute pancreatitis making it the most common gastrointestinal disease requiring acute hospitalization with costs for treatment exceeding \$2.5 billion annually<sup>[1]</sup>. The prognosis of patients with acute pancreatitis is largely determined by the presence of organ failure and infected pancreatic necrosis with associated mortality rates of 15%-30%<sup>[2]</sup>. Other complications of pancreatitis include systemic inflammatory response syndrome (SIRS), sepsis, and acute respiratory distress syndrome (ARDS). Despite the increasing incidence<sup>[3]</sup>, there is no current available pharmacologic therapy to mitigate the disease and its course. Current treatment of pancreatitis is largely supportive. Treatment of organ failure consists of organ supportive measures<sup>[4]</sup>, while treatment of infected pancreatic necrosis consists of drainage or

debridement and antibiotics<sup>[5]</sup>.

The most common causes of acute pancreatitis in the Western population are alcohol and gallstones, but many other causes have also been described and regardless of the trigger, there is an underlying common pathogenic outcome<sup>[6,7]</sup>. Acute pancreatitis is thought to be a local inflammatory process involving premature intra-cellular activation of digestive enzymes within acinar cells leading to autodigestion of the tissue that can progress to involve distant organs. The secretory acinar cells are also thought to release chemokines and cytokines that recruit leukocytes triggering an inflammatory response responsible for pancreatic edema and neutrophil accumulation<sup>[8]</sup>. This interstitial edema can sometimes progress to necrosis in parts of the pancreas and possible bacterial infection. Acute pancreatitis can also affect the microvascular circulation and compromise perfusion and oxygenation of the tissue<sup>[9]</sup>. While supportive therapy is largely the only treatment available for this disease, research in pancreatitis and a better understanding of the pathophysiology has led to the development of some pharmacologic therapies that target the various steps in the pathogenesis of pancreatitis. A review published in 2008 outlined some of the pharmacologic therapies investigated in experimental animal models<sup>[10]</sup>. Since then, some of those therapies have been further studied, new drugs have been found in each class of therapy, and more human clinical studies assessing the clinical utility of the therapies have been conducted.

This review focuses on the newer pharmacologic therapies for treatment of acute pancreatitis, and does not address the pharmacology of the standard treatment currently used such as pain control and antibiotics. The article summarizes the experimental, pre-clinical studies that provide evidence for the therapeutic potential for various classes of newer medications, outlines the clinical trials that have assessed their translational potential, and comments on future therapies and potential promising agents awaiting translation to clinical practice. This review focuses on pharmacologic therapy for acute pancreatitis that is not secondary to endoscopic retrograde cholangiopancreatography (ERCP).

## MOLECULAR PATHOGENESIS OF PANCREATITIS

Under physiologic conditions, inactive enzyme precursor secretion from the acinar cell occurs in response to cytosolic calcium. A sustained global elevation of this calcium, however, can lead to premature activation and secretion of digestive enzymes from the acinar cell, one of the earliest detectable events in pancreatitis<sup>[11]</sup>. After the initial insult to the pancreatic acinar cell, the disease progression is a multi-phase process that involves local inflammation of the pancreas, followed by a generalized inflammatory response, and the final stage of sepsis involving multi-organ failure in those with severe disease<sup>[8]</sup>. Following the initial injury, inflammatory cells are

often recruited to the pancreas *via* adhesion molecules, which can aggravate the inflammatory response leading to severe acute pancreatitis<sup>[8]</sup>. One of the key drivers of the inflammatory response in acute pancreatitis is likely circulating cytokines and chemokines. Active digestive enzymes are potent stimulators of macrophages, which subsequently induce the production of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukins<sup>[12]</sup>.

Cytokine production is governed by a large number of transcription factors, most prominent of which is nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B)<sup>[12]</sup>. The various types of cytokines released can cause their effects *via* highly specific cell surface receptors and stimulate enzymes such as cyclooxygenase-2 and inducible nitric oxide synthase (iNOS), which mediate the inflammatory process. Hence inhibition of these enzymes is likely to limit the local and systemic injury induced by pro-inflammatory leukocytes<sup>[12]</sup>. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) have also been implicated in the pathogenesis of acute pancreatitis. The mechanism by which these agents induce pancreatitis is two-fold. ROS and RNS act directly on biomolecules (lipids, proteins, and nucleic acids) and oxidize these components of cell membrane in the pancreas leading to membrane disintegration and necrosis of the pancreatic cells. In addition to the direct detrimental oxidative effects, ROS and RNS can also serve as secondary messengers in intracellular signaling and induce pro-inflammatory cascades<sup>[13]</sup>.

## PRECLINICAL STUDIES

### Anti-secretory agents

Acute pancreatitis is characterized by pancreatic and peripancreatic fat injury in part mediated by autodigestive enzymes. Excessive stimulation of the exocrine pancreas worsens acute pancreatitis<sup>[9]</sup> and thus is the rationale for testing anti-secretory agents as potential therapies for acute pancreatitis. Initial animal studies in the 1970s tested glucagon and subsequent studies investigated the use of somatostatin and long-acting somatostatin analogue.

Glucagon increases superior mesenteric artery blood flow and decreases pancreatic exocrine secretion<sup>[14]</sup>. A study utilizing a dog model of pancreatitis, however, did not find glucagon treatment alone or in combination with volume resuscitation to be better than volume resuscitation alone<sup>[15]</sup>. In fact in their model, pancreatic hemorrhage was associated with glucagon treatment suggesting possible worsening of the disease. A later study using pigs reported beneficial effects of glucagon<sup>[16]</sup> but other experimental studies in addition to the study mentioned above failed to support the use of glucagon therapy in experimental acute pancreatitis<sup>[17-19]</sup>.

Somatostatin is an inhibitory hormone with multiple effects on gastrointestinal motility and exocrine pancreas secretions<sup>[20]</sup>. One preclinical study using a taurocholate-induced rat model of acute pancreatitis, showed that so-

matostatin was effective in inhibiting basal and hormonal stimulated pancreatic enzyme secretion but did not affect the degree of pancreatic necrosis, pancreatic edema, leukocyte infiltration, or the enzyme content of the pancreas after pancreatitis was induced and did not lead to an overall decrease in mortality<sup>[21]</sup>. Another study showed that somatostatin stimulates hepatic and splenic reticulo-endothelial function in the rat hence suggesting benefit in the treatment of pancreatitis<sup>[22]</sup>. Preclinical studies have showed benefit of using somatostatin and its long-acting analogue, which provides the basis for the clinical trials discussed below.

The utility of anti-secretory agents has limitations given that the pancreas not only secretes enzymes, but also secretes bicarbonate and fluids, and animal studies have shown that stimulation of ductal secretion of bicarbonate has a protective effect on the severity of pancreatitis<sup>[23]</sup>.

### **Protease inhibitors**

Intrapancreatic activation of digestive enzymes plays an important role in the pathogenesis of acute pancreatitis. For this obvious reason protease inhibitors have been and remain of therapeutic interest in acute pancreatitis. Early studies in dogs with surgically-induced pancreatitis treated with trypsin inhibitors from egg white or soybean, and trasylol (aprotinin), a trypsin-kallikrein inhibitor from cattle were effective in suppressing acute pancreatitis<sup>[24]</sup>. Several other animal studies, including guinea pig model with taurocholate-induced necrotizing pancreatitis, also showed benefit with using protease inhibitors such as chlorophyll-a<sup>[25,26]</sup>. Interestingly however in the choline-deficient DL-ethionine (CDE) supplemented diet model of severe hemorrhagic pancreatitis, neither trasylol nor chlorophyll-a resulted in disease or mortality attenuation<sup>[27]</sup>. Despite the use of protease inhibitors at the time of CDE acute pancreatitis induction, the difference in rapidity, extent and intracellular protease release as well as the degree of and/or drug tissue penetration associated with the different experimental models might contribute to the observed opposing results<sup>[23]</sup>. Nevertheless, the later study has been more consistent with the clinical trial findings discussed below.

### **Anti-inflammatory and immunomodulators**

Altered products of arachidonic acid metabolism have been detected in experimental acute pancreatitis<sup>[28]</sup>. In acute pancreatitis thromboxane B levels are elevated whereas levels of prostaglandin E (PGE) are decreased. PGE therapy has been shown to have protective effects on the course of experimental acute pancreatitis in rodent models with taurocholate, CDE diet, or caerulein-induced pancreatitis<sup>[29-31]</sup>. Cyclo-oxygenase inhibitors such as indomethacin have been used to treat experimental acute pancreatitis with conflicting results in earlier studies<sup>[32]</sup> but subsequent studies have supported the beneficial effect of indomethacin particularly when used early or prior to disease induction in rat models with taurocholate-induced acute pancreatitis<sup>[33,34]</sup>. Similar to cyclo-

oxygenase, lipoxygenase is downstream of arachidonic acid and studies have shown that its inhibition in rat models with taurocholate-induced acute pancreatitis leads to reduced severity of the disease<sup>[35]</sup>. Leukotriene receptor antagonism however has shown to either worsen or have no effect on rat acute pancreatitis<sup>[33,36]</sup>, indicating the complexity of the pathway and the need for further in depth investigations.

Steroid therapy in acute pancreatitis has been of interest for several decades due to the associated leukocyte activation and release of inflammatory cytokines and chemokines during progression of acute pancreatitis. One experimental study in rat acute pancreatitis caerulein-induced showed that the effectiveness of steroid therapy depended on the severity of illness, with dexamethasone being more effective against pancreatitis with severe inflammation<sup>[37]</sup>. Another experimental study showed that dexamethasone reduced pancreatic damage when given prophylactically through reduction in intercellular adhesion molecule-1 expression, but was ineffective in preventing leukocyte recruitment into the pancreas when given therapeutically to rats with taurocholate-induced acute pancreatitis<sup>[38]</sup>. On the other hand, steroids have also been implicated as a cause of acute pancreatitis and some studies show that high-dose hydrocortisone can increase mortality rate and complication rates such as sepsis or infection<sup>[39-43]</sup>.

Animal studies have shown that interleukin-10 (IL-10), an anti-inflammatory cytokine, can ameliorate the severity of caerulein-induced acute pancreatitis in rodent models if given before or after the induction of disease<sup>[44]</sup>. IL-10 plays a protective role in the local and systemic consequences of the disease as IL-10 has been shown to block inflammation leading to improved outcome in experimental models<sup>[45]</sup>. Lexipafant, an antagonist of the platelet activating factor<sup>[46]</sup>, induces systemic effects and has been implicated as a mediator in the progression of acute pancreatitis<sup>[47]</sup>. Studies have shown that treatment of taurodeoxycholate and caerulein-induced rodent models of pancreatitis with lexipafant reduces the severity of pancreatitis-associated complications such as intestinal dysfunction, systemic IL-1 upregulation, and local leukocyte recruitment<sup>[48]</sup>. Lexipafant reduced acute pancreatitis associated inflammation<sup>[49]</sup> and improved acute necrotizing pancreatitis<sup>[50]</sup>. Despite beneficial outcomes with IL-10 and lexipafant in animal studies, their translation into clinical use has proven to be challenging.

### **Anti-oxidants**

Oxidative stress and injury is implicated in many inflammatory diseases. Oxygen-derived free radicals are generated in experimental acute pancreatitis<sup>[51]</sup> and there is evidence of decreased blood anti-oxidant levels in patients with severe acute pancreatitis<sup>[52]</sup>. These observations led to experimental studies that showed a protective effect of exogenously administered anti-oxidants such as selenium through reduction of pancreatic injury<sup>[53]</sup>. Pre-clinical studies in rodent models of acute pancreatitis induced by

a variety of methods, including carrageenan injection into pleural cavity or *L*-arginine hydrochloride, have shown reduced levels of glutathione and increased levels of oxidized glutathione suggesting a benefit from this intervention<sup>[54]</sup>. Clinical studies, which will be discussed later in detail, however have not been positive and it may be that anti-oxidants are more useful in prevention and/or as synergistic agents.

### Potential future promising therapeutic targets

One of the major limitations of preclinical studies is the uncertainty and lack of an ideal model that recapitulates all aspects of human disease. In addition preclinical therapies are often given either early or at the time of acute pancreatitis induction, when in reality patients often present with ongoing or late onset acute pancreatitis. Preclinical studies that demonstrate the efficacy of the therapy when administering the drug following disease progression are more likely to yield promising outcomes in clinical trials. With the exception of ERCP-induced acute pancreatitis in which prophylactic therapies can be instituted, it is unlikely that agents that interfere with initiation of acute pancreatitis are going to be effective but rather those that target the subsequent injury, repair or inflammatory pathways are likely to be beneficial in treating acute pancreatitis. For this reason, we discuss a few of the promising preclinical studies that target these pathways.

Inducible nitric oxide synthase activity is thought to be increased in experimental acute pancreatitis<sup>[55]</sup>. Experimental studies in the rat model have shown that agents such as *S*-methylisothiourea, an inducible nitric oxide synthase inhibitor, can decrease the bacterial translocation from gut into pancreatic necrosis thus reducing septic complications and mortality in acute pancreatitis<sup>[56]</sup>. Treatment with agents such as AR-C10222AA or *L*-N<sup>6</sup>-(1-iminoethyl)-lysine, highly selective iNOS inhibitors, early in the course after induction of acute pancreatitis, have also shown to have significant beneficial effects in acute pancreatitis in Australian possums<sup>[57]</sup> and may offer therapeutic benefit by decreasing pancreatic injury in future clinical studies.

Experimental studies with both pentoxifylline and heparin have shown a protective effect in rat models with acute pancreatitis. Studies have shown that pentoxifylline attenuates neutrophil activation, proinflammatory signalling, and systemic inflammation and cytokine levels in experimental acute pancreatitis especially when administered early<sup>[58]</sup>. Heparin has also been a pharmacologic therapy of recent interest with increasing number of reports suggesting its potential in the treatment of acute pancreatitis. Heparin was initially studied primarily for its ability to improve microcirculation, given that a disruption of the microcirculation contributes to the inflammatory process of acute pancreatitis. The anticoagulation mechanism of heparin is also associated with its anti-inflammatory effect in part secondary to reduced stimulation of macrophages and monocytes<sup>[59]</sup>. Experimental studies show that addition of heparin results in a decrease

of amylase, endothelin-1, and inflammatory cytokines such as TNF $\alpha$ , activation of NF- $\kappa$ B, and improved morphologic changes and vascular flow in the pancreas<sup>[60]</sup>. Such agents may enhance healing while dampening pro-inflammatory pathways, and may offer benefit in clinical acute pancreatitis.

Up-regulation of hemeoxygenase-1 (HO-1) or treatment with its downstream effectors and heme degradation products, biliverdin and carbon monoxide have protective effects in different rodent models of acute pancreatitis induced by taurocholate, caerulein, or CDE diet<sup>[61-66]</sup>. HO-1 overexpressing macrophages protect against acute pancreatitis<sup>[61,67]</sup>. Panhematin, an FDA-approved hemin formulation for acute intermittent porphyria, can prime HO-1 production<sup>[68]</sup>. Studies have shown that Panhematin if given before development of experimental pancreatitis can upregulate hemin-activated macrophages and lead to less pancreatic injury and if given after the development of acute pancreatitis, can also mitigate the extent of pancreatitis-related injury<sup>[63]</sup>. Notably, peripheral blood mononuclear cells from patients with mild acute pancreatitis have reversible HO-1 up-regulation that is associated with clinical recovery supporting therapeutic potential of HO-1 and the heme degradation products in patients with acute pancreatitis. Biliverdin *via* the aryl hydrocarbon receptor up-regulates IL-22<sup>[66]</sup>. There has been a lot of interest recently on the role of IL-22, a cytokine produced by hematopoietic cells that targets non-immune cells<sup>[69]</sup>. The pancreas interestingly has the highest expression of IL-22 receptor amongst any other tissue<sup>[69]</sup> and IL-22 treatment has been shown to ameliorate experimental acute pancreatitis<sup>[70]</sup>. Thus HO-1 and its downstream effectors are potential targets for clinical acute pancreatitis.

TNF $\alpha$  plays a central role in the pathogenesis of local and distant complications of acute pancreatitis<sup>[71]</sup>, and its blockade ameliorates experimental acute pancreatitis induced by caerulein, taurocholate, or CDE diet in mice studies<sup>[72,73]</sup>. Although there are theoretical increased risk of infectious complications with anti-TNF therapy, there are case reports with positive outcome in acute pancreatitis patients who received anti-TNF due to concomitant medical illness for which the anti-TNF therapy was indicated<sup>[74,75]</sup>. Thus with careful patient selection it is likely that anti-TNF therapy will yield beneficial results in clinical trials.

## CLINICAL STUDIES

Based on the pathophysiology of acute pancreatitis and the basic science research conducted providing evidence for promising pharmacologic therapy, many clinical studies have been performed assessing the effectiveness of these therapies including anti-secretory agents, protease inhibitors, immunomodulators, anti-inflammatory agents, and anti-oxidants.

### Anti-secretory agents

The use of glucagon for acute pancreatitis was first re-

ported in 1971 by Knight *et al*<sup>[76]</sup> and since then several subsequent uncontrolled clinical trials have shown a clinical improvement, decrease in pain, and a decline in enzyme activities in acute pancreatitis<sup>[77-79]</sup>. However, in a subsequent double-blinded trial of 69 patients glucagon was not found to have a significant impact on the mortality of the patients when compared to placebo<sup>[80]</sup>. Further clinical trials found no difference in mortality and morbidity such as pain and length of stay<sup>[81,82]</sup>.

Atropine was also studied in a randomized clinical trial but did not have a significant effect on the clinical course of patients when compared with no treatment<sup>[83]</sup>. Infusion of salmon calcitonin was also thought to strongly depress gastric secretions such as gastric acid, pepsin, and gastrin<sup>[84-86]</sup> as well as pancreatic enzyme secretions stimulated by various secretagogues without affecting the fluid and electrolyte secretions<sup>[87]</sup> thus mitigating the pathogenesis of acute pancreatitis<sup>[88]</sup>. A multicentered randomized double-blinded trial assessing the use of synthetic salmon calcitonin in acute pancreatitis showed that though mortality was not affected, the number of patients without pain and normalized serum amylase was higher in the treated group as compared to the placebo group. Other parameters such as analgesic dose, leukocyte count, and normalization of seven clinical and laboratory criteria showed a positive trend in the treated group but was not clinically significant<sup>[88]</sup>.

Clinical trials have well studied the use of somatostatin for treatment of acute pancreatitis given that it inhibits pancreatic exocrine secretions, reduces splanchnic blood flow, stimulates the hepatic reticuloendothelial system, and modulates the inflammatory cytokine cascade<sup>[89]</sup>. However, several randomized clinical trials failed to show a clinically significant benefit with the use of somatostatin<sup>[90-94]</sup>. A meta-analysis of seven publications, on the other hand, did show an overall mortality benefit with somatostatin for severe acute pancreatitis (OR = 0.36, 95%CI: 0.2-0.64) but there was no significant decrease in complication rates in patients with acute pancreatitis<sup>[95]</sup>.

Octreotide, a synthetic analogue of somatostatin, was also tested clinically. While initial small studies did not show any overall mortality benefit, they suggested a decrease in severity of acute pancreatitis, reduced local complications, and earlier return to oral intake<sup>[96]</sup>. One of the largest clinical trials of 302 patients with moderate to severe pancreatitis however did not show any clinical benefit<sup>[97]</sup>, but a smaller study of 50 patients with severe acute pancreatitis showed a clinically significant reduction in sepsis (76%-24%), ARDS (56%-28%), hospital stay (33.1-20.6 d), and mortality (8-2 deaths)<sup>[98]</sup>. While an older meta-analysis performed did suggest a mortality benefit for severe acute pancreatitis (OR = 0.57, 95%CI: 0.35-0.88)<sup>[95]</sup>, another more recent meta-analysis that limited their estimate to four higher quality studies did not show any benefits in sepsis, mortality, or complication rates<sup>[99]</sup>.

Thus clinical studies assessing the use of anti-secretory agents have provided inconclusive evidence on their ben-

efits. There appears to be no benefit with the use of these agents in mild acute pancreatitis, and the benefits are uncertain in severe acute pancreatitis. Hence these agents are not currently recommended in clinical practice<sup>[4,100]</sup>.

### Protease inhibitors

One of the earliest protease inhibitors studied is aprotinin, and initial studies showed some benefit in mortality though subsequent studies have failed to repeat such results<sup>[101,102]</sup>. Studies delivering aprotinin *via* peritoneal lavage have shown less necrosis in the treatment group with a reduction in complement activation (specifically less C3a and more C1 inhibitor plasma levels) but no overall difference in mortality<sup>[103-105]</sup>. Aprotinin may still have a role in treating acute pancreatitis given that it was not given in high enough doses to produce sufficient inhibition of protease activity and the studies were not adequately powered<sup>[106]</sup>.

Gabexate mesilate is a smaller protease inhibitor that has been studied in human clinical trials<sup>[107]</sup>. While early smaller clinical studies suggested a mortality benefit with the administration of this therapy<sup>[108,109]</sup>, a larger randomized controlled trial of patients with moderate to severe acute pancreatitis found no clinical benefit<sup>[110,111]</sup>. Two other meta-analyses also demonstrate this lack of mortality benefit, though they showed a decreased need for surgery and less complications<sup>[95,112]</sup>. A recent study showed some benefit in gabexate when delivered through continuous regional arterial infusion (CRAI)<sup>[113]</sup>.

Nafomostat is a newer synthetic protease inhibitor a hundred times more potent than gabexate<sup>[107]</sup>. Clinical studies assessing the delivery of nafomostat *via* CRAI along with antibiotics have shown greater mortality benefit and lower incidence of necrosis with earlier administration of the drug<sup>[114]</sup>. Studies have also shown that delivery of the drug *via* CRAI compared to non-CRAI decreases the need for surgery and improves survival<sup>[115,116]</sup>.

None of the protease inhibitors mentioned above are currently part of standard clinical care for acute pancreatitis treatment as larger and adequately powered studies are needed prior to their recommendation for clinical use. Nafomostat, however, has the most promise out of the three particularly when given *via* CRAI in combination with antibiotics.

### Immunomodulators

Based on the preclinical positive results, Lexipafant was tested in clinical trials in patients with severe acute pancreatitis. The first clinical trial assessing the use of this therapy did not show a difference in mortality but showed a reduction in organ failure<sup>[117]</sup>. Another study showed significantly less organ failure, a reduction in mortality and SIRS<sup>[118]</sup>. The largest randomized clinical trial involving this therapy, however, showed no significant reduction in organ failure or local complications leading to the conclusion that lexipafant alone cannot treat severe acute pancreatitis<sup>[119]</sup>.

Dotrecogin alfa, an analogue of endogenous protein

C, has shown some benefit in the treatment of acute pancreatitis<sup>[120]</sup>. Endogenous protein C is made in the liver and inhibits thrombin formation and facilitates thrombolysis. Given that lower levels of activated protein C are associated with higher mortality in acute pancreatitis, activated protein C was thought to mitigate severe acute pancreatitis by modulating the immune system through regulating leukocyte endothelial interaction and mitogen-activated kinases and improving intestinal microcirculation<sup>[121]</sup>. Initial case reports showed some benefit in using dotrecogin alfa in acute pancreatitis<sup>[122]</sup>, but a subsequent pilot study did not show any clinically significant difference with the use of dotrecogin alfa<sup>[123]</sup>.

### Anti-inflammatory agents

Indomethacin, which inhibits phospholipase A2 activity and cyclooxygenase activity thus decreasing neutrophil mediated inflammation, has been clinically studied based on earlier pre-clinical studies<sup>[124]</sup>. One study assessing this therapy however, only reported decreased pain and opiate use when given to patients with acute pancreatitis<sup>[125]</sup> suggesting analgesia but not anti-inflammatory related benefits. So far benefits of indomethacin have been largely limited to post-ERCP pancreatitis<sup>[126]</sup>.

Steroid therapy is widely used to dampen inflammation in various organ systems. Though steroid therapy has been shown to be beneficial in the treatment of autoimmune pancreatitis<sup>[127]</sup>, in acute pancreatitis however steroid therapy has been implicated in disease induction<sup>[128]</sup>. A postmortem study done by Carone and Liebow showed histologic evidence of acute pancreatitis or peri-pancreatic fat necrosis in 16 out of 54 patients treated with steroids<sup>[129]</sup>. Initial case reports have also linked the use of steroids with acute pancreatitis<sup>[130]</sup>. Studies have also shown that corticosteroids have no beneficial effect in the prevention of post-ERCP pancreatitis<sup>[131]</sup>. However, given that some pre-clinical studies suggest that steroids can reduce the inflammatory cascade, leukocyte recruitment, and subsequent pancreatic damage when given prophylactically<sup>[38]</sup>, further well-designed studies are warranted.

### Anti-oxidant agents

Several clinical trials have assessed the benefit of anti-oxidant agents in acute pancreatitis given the role of reactive oxygen species and cellular injury in acute pancreatitis as well as the evidence generated by pre-clinical studies. Anti-oxidant agents studied include n-acetylcysteine, methionine, beta-carotene, selenium, ascorbic acid, and alpha-tocopherol.

A randomized clinical trial assessing treatment with acetylcysteine, selenium, and vitamin C showed increased serum levels of anti-oxidants and decreased markers of oxidative stress but no improvement in organ dysfunction<sup>[132]</sup>. Another study with patients receiving Vitamin C, n-acetylcysteine, and other anti-oxidants showed no significant difference in complications or length of hospital stay<sup>[133]</sup>. The third recent clinical study with vitamins A,

C, and E also showed no significant difference in organ dysfunction<sup>[134]</sup>.

Studies assessing the use of glutamine, a more potent anti-oxidant, have been more promising. One study randomizing 80 patients to glutamine showed decreased number of complications, length of stay, need for surgery, and mortality when administered early after hospitalization<sup>[135]</sup>. A meta-analysis of randomized control trials with glutamine showed a mortality benefit (RR = 0.3, 95%CI: 0.15-0.6) and reduced infectious complications (RR = 0.58, 95%CI: 0.39-0.87), but no difference in length of hospital stay. The benefit with glutamine was observed only in patients receiving total parenteral nutrition<sup>[136]</sup>. Thus the role of anti-oxidant therapy in acute pancreatitis remains to be determined.

### Other therapies

A variety of other therapies for acute pancreatitis have also been assessed in clinical studies. Antifibrinolytics such as epsilon-aminocaproic acid (EPCA) has been thought to ameliorate the pathogenesis of acute pancreatitis by inhibiting the activation of plasminogen, plasmin, and trypsin, by inhibiting pancreatic kallikrein, and by increasing serum antitrypsin activity<sup>[137]</sup>. A clinical study assessing the use of EPCA and aprotinin in acute pancreatitis, however, did not have any clinically significant improvement on outcomes such as hospital duration and normalization of laboratory values compared to the conventional treatment group and the aprotinin treated groups<sup>[138]</sup>.

Fresh frozen plasma (FFP) has also been assessed in the treatment of acute pancreatitis given laboratory studies that showed the inhibitory effect of FFP on proteolytic activity in the serum of patients with acute pancreatitis<sup>[139]</sup>. While one initial prospective pilot clinical study showed a decrease in mortality with the administration of FFP in patients with acute pancreatitis when administered during the first five days of illness onset<sup>[139]</sup>, a larger multi-centered controlled clinical trial showed no improved clinical outcome in the group given FFP as opposed to colloids treated group<sup>[140]</sup>.

Molecular pathways under target development include the kallikrein-kinin and complement system given that severe acute pancreatitis is associated with elevated C3a and sC5b-9 levels<sup>[141]</sup>. C1 esterase inhibitor blocks a variety of proteolytic enzymes including activated C1 complex and kallikrein<sup>[142]</sup>, and both experimental studies as well as small human studies have shown that C1 esterase inhibitor has some protective benefit in severe acute pancreatitis<sup>[143]</sup>. Currently pharmacologic targets of the complement system are used in a variety of other diseases such as hereditary angioedema, paroxysmal nocturnal hemoglobinuria, and hemolytic uremic syndrome<sup>[144]</sup> that may permit more rapid translation.

## CONCLUSION

Both pre-clinical and clinical studies (Tables 1 and 2) have

**Table 1 Summary of pharmacologic agents studied in experimental acute pancreatitis**

| Pharmacologic agent                      | Animal model |   | Outcome assessment  | Citations   |
|--|--------------|---|---|-------------|
|  | Species name | Mechanism of pancreatitis induction   |   |             |
| Anti-secretory agents                    |              |   |   |             |
| Glucagon                                 | Dog          | Duodenal obstruction, pancreatic duct infusion of lactated ringer solution or pancreatic duct infusion of bile-trypsin solution | Not beneficial when compared to simple volume resuscitation | [15]        |
|  | Pig          | Hemorrhagic pancreatitis induced by bile injection into pancreatic duct   | Reduced mortality   | [16]        |
| Somatostatin                             | Rat          | Taurocholate  | No decrease in mortality                                    | [21, 22]    |
| Protease inhibitors                      |              |   |   |             |
| Aprotinin                                | Dog          | Hemorrhagic pancreatitis surgically induced   | Prophylactic and therapeutic potential                      | [17-19]     |
| Chlorophyll-a                            | Guinea pig   | Taurocholate-induced necrotizing pancreatitis   | Benefit in survival   | [25-27]     |
| Anti-inflammatory/<br>immunomodulators   |              |   |   |             |
| PGE therapy                              | Rat, mice    | Taurocholate, CDE diet, or caerulein  | Protective effect   | [29-31]     |
| Indomethacin                             | Rat          | Olive oil or taurocholate   | Beneficial particularly early in induction                  | [32-34]     |
| Lipoxygenase inhibitor                   | Rat          | Taurocholic acid  | Protective effect   | [35]        |
| Steroid                                  | Rat          | Caerulein and taurocholate  | Decreased inflammation and protective                       | [37-43]     |
| IL-10                                    | Rat, mice    | Caerulein   | Reduction in severity of disease                            | [44, 48-50] |
| Lexipafant                               | Rat, mice    | Intraductal administration of 5% sodium taurodeoxycholate or caerulein  | Reduction in severity, SIRS, and bacterial translocation    | [46, 47]    |
| Hemin/panhematin/<br>biliverdin/CO/IL-22 | Rat, mice    | caerulein, taurocholate, or CDE diet  | Protective and therapeutic effects                          | [61-67]     |
| Anti-TNF alpha                           | Mice         | caerulein, taurocholate, or CDE diet  | Decreased inflammatory response and cell death              | [72-75]     |
| Anti-oxidants                            |              |   |   |             |
| Tempol                                   | Mice         | carrageenan injected into pleural cavity  | Decrease in inflammation and shock                          | [54]        |
| Selenium                                 | Rat          | L-arginine hydrochloride  | Reduction in pancreatic injury                              | [53, 145]   |

CO: Carbon monoxide; PGE: Prostaglandin E1; SIRS: Systemic inflammatory response syndrome; TNF $\alpha$ : Tumor necrosis factor  $\alpha$ ; CDE: Choline deficient ethionine-supplemented.

shown promising opportunities for novel pharmacologic therapy for acute pancreatitis that can supplement the traditional treatment involving supportive measures such as fluid resuscitation, nutritional support, pain control, and antibiotics as needed. Pre-clinical and clinical studies have shown promise in a variety of classes of therapies that include anti-secretory agents, protease inhibitors, immunomodulators and anti-inflammatory agents, and anti-oxidants. While some of the evidence for these therapies still remains inconclusive and hasn't been translated into current standard treatment care, there exists a tremendous potential therapeutic benefit as demonstrated in these studies. The immunomodulating pharmacologic therapies also have yet to be translated into standard clinical care for acute pancreatitis<sup>[67]</sup>.

There are also new targets for pharmacologic therapy that can expand the potential therapies for acute pancreatitis. Strategies that alter the activity of key immune cells in the inflammatory cascade triggered by acute pancreatitis offer great potential<sup>[67]</sup>. Other molecular targets such as those that interfere with the kallikrein-kinin, proteolytic, and complement system as discussed with further development have the potential of being applied to acute pancreatitis as well in the future. In addition to expanding targets for pharmacologic therapy, existing therapies need to be better studied in clinical trials in the future.

Experimental pre-clinical studies have identified several therapies that have not proven to be effective in clinical trials and thus have not been translated to the clinical arena. One of the reasons for this discrepancy may be that in the animal models, the pharmacologic therapy is often administered prior to when pancreatic injury ensues thus providing evidence that the therapy can provide a protective but not necessarily therapeutic effect.

In the clinical studies, however, the medication of interest is often tested once the pancreatic injury has already occurred and the inflammatory cascade induced by acute pancreatitis has already initiated. In the future, better design of clinical trials that deliver the treatment earlier from symptom onset can maximize the drug's ability to interrupt the inflammatory cascade and yield better results. Clinical trials need to also be standardized with respect to eligibility criteria, supportive treatment approaches, and outcomes measured. Clinically meaningful primary and secondary outcomes such as mortality, organ failure, SIRS, pancreatic necrosis, and local complications, length of hospital stay, requirement for pain medications, quality of life, and cost of care should be clearly outlined.

Despite the inconclusive evidence in therapeutic benefit seen with many of the pharmacologic therapies for acute pancreatitis studied thus far, there exists great need and promise in the development of effective pharmaco-

**Table 2** Summary of pharmacologic agents studied in clinical acute pancreatitis

| Pharmacologic agent                              | Study design      | Sample size | Outcome assessment                                    |  |                          |                     |   | Citations  |
|--|-------------------|-------------|---|--|--------------------------|---------------------|---|------------|
|  |                   |             | Decreased SIRS  | Decreased organ failure  | Decreased length of stay | Decreased mortality | Other   |            |
| Anti-secretory agents                            |                   |             |   |  |                          |                     |   |            |
| Glucagon   | RCT               | 22-69       | Not reported  | Not reported   | No                       | No                  |   | [76-82]    |
| Atropine   | RCT               | 51          | Not reported  | Not reported   | No                       | No                  |   | [83]       |
| Calcitonin                                       | RCT               | 94          | Not reported  | Not reported   | Not reported             | No                  | ↓ pain, earlier normalization of labs                   | [84-86]    |
| Somatostatin                                     | RCT/meta-analysis | 50-703      | Not reported  | Indeterminate (no effect on multi-organ failure but ↓ local complications) | Indeterminate            | Indeterminate       | ↓ pancreatic abscess and necrosis, ↓ local inflammation | [90-95]    |
| Octreotide                                       | RCT/meta-analysis | 19-948      | Yes   | Yes  | Indeterminate            | Indeterminate       |   | [97-99]    |
| Protease inhibitors                              |                   |             |   |  |                          |                     |   |            |
| Aprotinin  | RCT               | 48-105      | Not reported  | No   | Yes                      | No                  | ↓ pancreatic necrosis, ↓ complement activation          | [101-105]  |
| Gabexate mesilate                                | RCT/meta-analysis | 42-898      | Not reported  | No   | No                       | No                  | CRAI ↓ hospitalization stay and SIRS                    | [108-113]  |
| Nafomostat                                       | RCT               | 51-78       | Not reported (↓ pancreatic necrotic tissue infection) | Not reported   | Not reported             | Yes                 | Only CRAI + abx has benefit                             | [114-116]  |
| Immunomodulators                                 |                   |             |   |  |                          |                     |   |            |
| Lexipafant                                       | RCT               | 50-290      | Yes   | Yes  | Not reported             | Yes                 | ↓ local complications (pancreatic abscess, pseudocyst)  | [117-119]  |
| Dotrecogin alfa                                  | RCT               | 32          | Yes   | No   | Not reported             | No                  |   | [122, 123] |
| Acetylcysteine, selenium, vitamin C combinations | RCT               | 39-53       | Indeterminate (↓ CRP but not sig)                     | No (trend toward ↑ MOF)  | No                       | No                  |   | [132-134]  |
| Glutamine  | RCT/meta-analysis | 505         | Yes   | Yes  | No                       | Yes                 |   | [135, 136] |

RCT: Randomised controlled trials; SIRS: Systemic inflammatory response syndrome; CRAI: Continuous regional arterial infusion; ERCP: Endoscopic retrograde cholangiopancreatography; MOF: Multiple organ failure; RCT: Randomized controlled trial.

logic therapy for acute pancreatitis. Better understanding of the pathophysiology of the disease and lessons learned from past clinical studies offer a great foundation upon which to expand such that the current management of pancreatitis largely characterized by supportive therapy can eventually be transitioned to not only preventive but also to reparative and effective therapy. Better characterization and standardization of the patient population, along with well controlled and adequately powered clinical studies tied to standardized outcomes, will ensure a reliable and valid assessment of the therapeutic role of preclinical tested agents.

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