Pharmacologic Therapy

11

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Introduction

Acute pancreatitis is one of the most common gastrointestinal diseases, with a continuum of severity [1]. Mild pancreatitis is self-limiting and exists when there is no evidence of organ failure and/or pancreatic necrosis. Moderate severe pancreatitis is defined by local complications without persistent (>48 h) organ failure. Severe pancreatitis occurs when persistent organ failure develops [2]. Mild acute pancreatitis is the most common clinical presentation with moderate morbidity and negligible mortality. In contrast, severe acute pancreatitis occurs in up to 20 % of patients and is associated with significant morbidity and mortality [3].

Because of this difference in morbidity and mortality, the benefits of pharmacologic therapy will have the greatest impact in patients with severe acute pancreatitis. For mild disease, it may further reduce the development of organ failure and local complications. It may lead to earlier feeding, less narcotic pain medication use, and shorter hospitalization. For severe disease, it may alter the natural history, including the development of chronic pain, chronic pancreatitis, and hospital-related mortality.

Non-pharmacological interventions, including appropriate IV fluid administration (Chap. 8), antibiotic use (Chap. 9), and timely nutrition (Chap. 10), have already been discussed.

There is currently no U.S. Food and Drug Administration (FDA) approved pharmacological therapy for the treatment of acute pancreatitis. This chapter has three objectives (Table 11.1). The first objective will review key aspects of the pathophysiology of acute pancreatitis to highlight potential targets for pharmacologic intervention. The second objective will review pharmacologic therapies that have been evaluated. The third objective will highlight potential novel targets for future development.

Pathophysiology Overview: Potential Therapeutic Targets

When considering pharmacological therapies for acute pancreatitis, it is helpful to briefly outline the current pathophysiological framework for acute pancreatitis (Fig. 11.1). The primary site of injury occurs at the acinar cell from aberrant trypsin activity. Whether the mechanism is mechanical, metabolic, and/or genetic, the insult injures the acinar cell by blocking normal secretory activity [4]. Specifically, normal apical exocytosis is blocked and basal exocytosis (which under normal circumstances is constitutively blocked) now occurs. During this period of

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Table 11.1 Three objectives of this chapter

1. Review key pathophysiological aspects of acute pancreatitis to highlight potential pharmacological interventions
2. Summarize past clinical trials/studies of pharmacological agents studied for acute pancreatitis
3. Define potential novel targets for future development

dysregulation, the inactive trypsinogen within these secretory vesicles converts into active trypsin within the acinar cell. The actual site of intracellular activation remains elusive but proposed compartments include lysosomes/endosomes, autophagic vacuoles, and secretory granules. The immune system plays a pathophysiologic role in this early cascade that includes accelerating injury by stimulating zymogen activation within the acinar cell or limiting injury by degrading zymogens that are inappropriately released from the basolateral membrane of the acinar cell [5].

Acinar cell injury with inappropriate and excess leakage of activated enzymes subsequently induces local inflammation by various mechanisms. Activated proteases damage the vascular endothelium leading to microcirculatory injury. Leukocytes arrive via chemoattraction from increased vascular cell adhesion molecule 1 (VCAM-1) and intercellular cell adhesion molecule 1 (ICAM-1) expression. The complement system is also activated and contributes to further injury. Both activated pro-inflammatory and anti-inflammatory cytokines lead to propagation of acinar cell injury and local inflammation. Specific pro-inflammatory cytokines include interleukin-1 (IL-1), IL-6, IL-8, tumor necrosis factor (TNF), and platelet-activating factor (PAF). Specific anti-inflammatory cytokines include IL-2, IL-10, and IL-11. Other inflammatory mediators include arachidonic acid metabolites, reactive oxygen metabolites, and nitric oxide.

Unabated local inflammation can lead to systemic inflammation. The mechanism for this transition is thought to occur when activated pancreatic proteases reach the liver via the portal vein and induce hepatic injury. Hepatic injury stimulates the Kupffer cells (macrophages) within the liver to further activate pro-inflammatory cytokines and mediators triggering a systemic response. This clinically correlates with development of the systemic inflammatory response syndrome—a sensitive predictor for severe acute pancreatitis [6]. Acute phase proteins including C-reactive peptide and IL-6 are systemically released contributing to multi-organ failure. Bacterial translocation via the intestine occurs later in the course of disease leading to infected necrotizing pancreatitis.

The immune system plays a significant pathophysiological role in this disease. The initial inflammatory response in acute pancreatitis is characterized by up-regulation of ICAM-1 and neutrophil recruitment. Consequently, ICAM-1 deficiencies and neutrophil depletion in animal models have demonstrated a reduction in acute pancreatitis severity [7]. Regulating the degree of macrophage activation, which in turn induces more cytokine and inflammatory mediators such as TNF, IL-1B, IL-6, monocyte chemotactic protein (MCP)-1, and PAF may represent another pharmacological target to arrest local inflammation. Previous animal model studies have shown macrophage depletion to protect against experimental pancreatitis [8]. Certain subsets of activated T cells also appear to be important for progression to severe acute pancreatitis. Subsequent depletion may prevent progression to systemic disease [9].

More germane to severe acute pancreatitis are the extra-pancreatic immune responses that may be targeted for pharmacological intervention. Pancreatic necrosis, particularly when infected, is a major cause of morbidity and mortality. Control of bacterial translocation from the intestine may be regulated by toll-like receptors (TLRs), other nucleotide-binding domain and leucine-rich repeat-containing molecules, and dendritic cells [10]. Previous animal models have shown TLR4 deficiency to be associated with less severe forms of pancreatitis [11]. The role of TLRs is complex and incompletely understood, as various polymorphisms in TLRs have been associated with increased susceptibility to acute pancreatitis [12]. A better understanding of the regulatory role of the immune system within these local and systemic

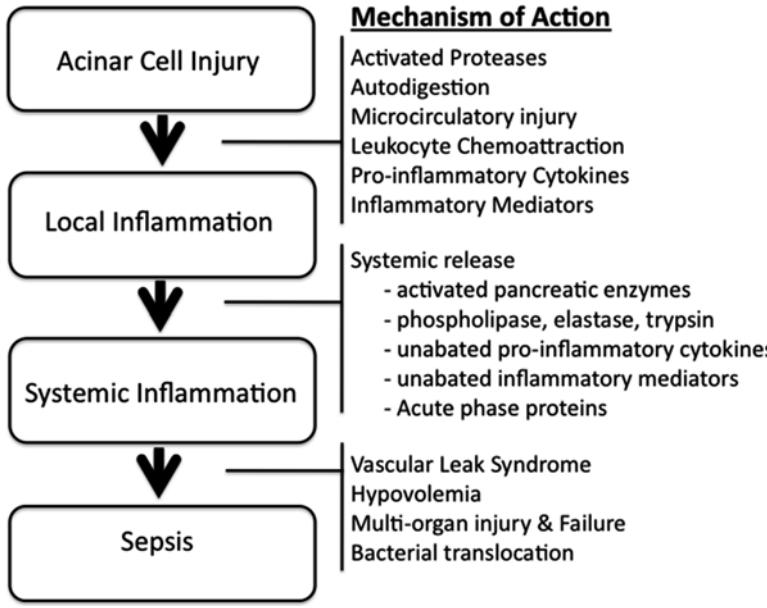

Fig. 11.1 Mechanisms of action involved in the pathophysiology of severe acute pancreatitis

inflammatory mechanisms that give rise to severe acute pancreatitis may lead to effective pharmacological intervention.

The complement system also appears to significantly contribute to the pathogenesis of acute pancreatitis. While complex and incompletely understood, it appears to be activated early in acute pancreatitis and to a greater extent in severe acute pancreatitis. Evidence of an activated complement system leading to severe pancreatitis is demonstrated by the observation of elevated C3a and sC5-9 levels in severe acute pancreatitis [13]. The elevation of C5a is particularly interesting because while it is commonly recognized as a potent pro-inflammatory mediator, it has demonstrated anti-inflammatory properties in experimental acute pancreatitis [14]. In such models, the use of a soluble complement receptor-1 demonstrated decreased leukocyte adhesion leading to a less severe course of acute pancreatitis [15].

The Kallikrein-Kinin system may also be involved in the pathogenesis of acute pancreatitis [14, 16, 17]. This poorly understood system involves the release of biologically active peptides, including bradykinin and kallidin. The pancreas has one of the highest tissue concentrations of these peptides compared to other organs. These peptides mediate large and small artery vasodilation and increase vascular permeability in the capillaries. This may facilitate capillary leakage and the pro-inflammatory mechanisms of acute pancreatitis. These peptides may also affect the afferent nervous system and may play an important role in pain development during acute pancreatitis. The development of kallikrein inhibitors may lead to decreased tissue damage, sepsis, and pain.

While many questions remain, our understanding of the pathophysiology of acute pancreatitis has advanced significantly. Beginning with acinar cell injury, this increased understanding has delineated a complex and interrelated system that includes a broad array of immunological mediators that define the course of disease. This framework provides a rational-based foundation toward developing therapeutic interventions for preclinical and clinical studies. As our understanding increases further, the number of potential pharmacological targets will also increase giving further hope for novel treatments. The subsequent section will review previously studied pharmacological agents in clinical studies.

Pharmacological Agents: Previous Clinical Studies

Based on the understood pathophysiology of acute pancreatitis and promising observations in preclinical studies, several clinical studies of pharmacological agents for acute pancreatitis have been performed. These studies can be categorized by the purported mechanism of intervention within the pathophysiological framework including anti-secretory agents, protease inhibitors, immunomodulators, anti-inflammatory agents, and antioxidants (Table 11.2) [18, 19].

Anti-secretory Agents

A long-time initial management principle of acute pancreatitis involves no per oral intake to minimize pancreatic secretions. Consequently, pharmacological agents that decrease pancreatic secretions have been studied in human clinical trials beginning in the late 1970s. Some of the first reported clinical trials involved the use of glucagon [20–22]. These included three randomized trials of sample sizes ranging between 22 and 69 patients with variable severity and etiologies of pancreatitis. No difference in mortality and relevant morbidities such as pain and length of stay was observed. Atropine and calcitonin

Table 11.2 Summary of pharmacological agents studied in clinical trials for acute pancreatitis

Pharmacological agent	Study design	Sample size	Outcomes assessment	Citation
Anti-secretory agents				
Glucagon	RCT[a]	22–69	No significant benefit	[20–22]
Atropine	RCT	51	No significant benefit	[23]
Calcitonin	RCT	94	No significant benefit	[24]
Somatostatin	RCT/meta-analysis	50–703	Possible less morbidity in SAP[b]	[26–31]
Octreotide	RCT/meta-analysis	19–948	Mixed results. Possible less morbidity in SAP	[31, 32, 34–40]
Protease inhibitors				
Aprotinin	RCT	48–105	No consistent significant benefit	[44–46]
Gabexate mesilate	RCT/meta-analysis	42–898	No consistent significant benefit	[31, 50, 52–54, 106]
Nafomostat (with antibiotics)	RCT	51–78	Mortality benefit for SAP by CRAI[c]	[56–59]
Immunomodulators				
Lexipafant	RCT	50–290	No consistent significant benefit	[62–64]
Dotrecogin alfa	RCT	32	No significant benefit	[68]
Antioxidants				
Combinations[d]	RCT	39–53	No significant benefit	[70–72]
Glutamine	Meta-analysis	505	Mortality benefit in patients on TPN	[75]
Anti-inflammatory				
Indomethacin	RCT	30	No significant benefit	[78]

[a]Randomized controlled trials
[b]Severe acute pancreatitis
[c]Continuous regional arterial infusion
[d]*n*-Acetylcysteine, vitamin C, vitamin A, selenium, and vitamin E

have also been studied, each in a randomized controlled trial, without benefit compared to placebo [23, 24].

Produced in the gastrointestinal tract, somatostatin is thought to have several beneficial effects in acute pancreatitis. These include inhibiting exocrine pancreatic secretions, reducing splanchnic blood flow, stimulating the hepatic reticuloendothelial system, and modulating the cytokine cascade [25]. Somatostatin has been well studied as a pharmacological agent in human clinical trials for acute pancreatitis [26–30]. While there is slight variability in the dose and duration of somatostatin, four different randomized controlled trials of 50–100 patients failed to show a clinically significant benefit with somatostatin treatment.

One particular study by Planas and colleagues focused specifically on patients with severe acute pancreatitis in the intensive care unit [30]. They randomized 50 patients to somatostatin for 10 days versus placebo in an unblinded fashion. While there was no difference in mortality or length of stay, they observed a reduction in the need for surgery for local complications (45.8 % vs. 86.4 %; $p=0.005$). A meta-analysis that included seven additional non-English publications (three were abstracts and half of which were not randomized) reported an overall mortality benefit with somatostatin for severe acute pancreatitis with an odds ratio (OR) of 0.36 (95 % CI: 0.20–0.64). Interestingly, this analysis did not find a correlating significant decrease in complication rates with somatostatin use. Further, the authors describe assessing for heterogeneity in their methods section, but did not report it in the results or discussion raising a concern regarding the validity of these results [31].

Octreotide is a synthetic analogue of somatostatin that can be given both by intravenous infusion (IV) and subcutaneously (SC). There are several clinical trials that have studied its efficacy for acute pancreatitis [32–38]. The first several studies were small and while they showed no mortality benefit, there was suggestion of decreased severity, local complications, and earlier return to oral intake [32, 34, 35, 39]. Uhl and colleagues published the largest clinical trial of 302 patients with moderate-severe pancreatitis from 32 centers and no clinical benefit was observed [36]. In a much smaller study by Paran and colleagues of 50 patients with severe acute pancreatitis, a significant reduction in sepsis (24 % vs. 76 %, $p=0.002$), acute respiratory distress syndrome (28 % vs. 56 %, $p=0.04$), hospital stay (20.6 days vs. 33.1 days, $p=0.04$), and mortality (2 deaths vs. 8 deaths, $p<0.019$) was reported [37]. More recently Yang and colleagues randomized 161 obese patients (BMI > 25) with mild pancreatitis to octreotide IV infusion for 3 days versus placebo and reported a risk ratio of 0.27 (95 % CI: 0.1–0.69) for developing severe pancreatitis. They also reported a difference in local complications in favor of octreotide treatment (4.9 % vs. 19 %, $p=0.006$) [38]. Although a meta-analysis performed by Andriulli and colleagues [31] suggests a mortality benefit for severe acute pancreatitis (OR 0.57 [95 % CI: 0.35–0.88]), another more recent meta-analysis [40] that limited their estimate to four higher quality studies [30, 34, 36, 37] did not show any benefit in sepsis, complication rates, or mortality. However, one of the four studies [30] did not specifically look at octreotide but somatostatin.

Although studied over the past 30 years, the use of anti-secretory agents, specifically somatostatin and octreotide, has produced inconsistent results. There appears to be no benefit in mild acute pancreatitis. For severe acute pancreatitis, the reported benefits remain inconclusive such that it is not currently recommended in clinical practice [3, 41].

Protease Inhibitors

The use of protease inhibitors for treating acute pancreatitis has been proposed and reported in clinical studies as far back as nearly 50 years ago [42]. The rationale stems from premature and excess protease activation within the pancreatic parenchyma leading to autodigestion and subsequent inflammation. While endogenous inhibitors exist to mitigate these events, clinically severe disease occurs when these defense

mechanisms are overwhelmed leading to a systemic inflammatory response syndrome.

Aprotinin, a bovine pancreatic trypsin inhibitor, was one of the first protease inhibitors described for treating acute pancreatitis in humans with reported benefit in mortality [42–44]. However, subsequent studies have failed to repeat such a benefit. Baldin and colleagues randomized 55 patients with severe acute pancreatitis to peritoneal lavage of aprotinin and reported no difference in mortality or other relevant clinical outcomes [45]. Berling and colleagues also studied peritoneal lavage delivery of aprotinin in 48 patients with severe acute pancreatitis. Despite reporting less necrosis in the aprotinin-treated group, they observed no difference in mortality [46]. In further studying this difference in necrosis, they observed a reduction in complement activation with aprotinin. Specifically, the treated groups had relatively less C3a and more C1 inhibitor plasma levels [47]. They also observed no difference in the plasma levels of leukocyte proteases and postulated that this may explain the lack of mortality benefit with aprotinin given as a peritoneal lavage. Recently, Smith and colleague reviewed the literature and concluded that aprotinin may still have a role in treating acute pancreatitis because the previous studies were not adequately powered, and that aprotinin was not given in high enough doses to produce sufficient inhibitory activity [48].

In contrast to aprotinin, gabexate mesilate is a smaller protease inhibitor that has been studied in humans based on promising preclinical studies [49]. Early clinical studies including a small controlled trial of 42 patients suggested a trend towards a mortality benefit [50, 51]. However, larger randomized controlled trials including a multi-center study that randomized 223 patients with moderate to severe acute pancreatitis found no clinical benefit [52, 53]. Two different meta-analyses published in 1998 and 2003 reiterate this finding of no mortality benefit [31, 54]. The earlier meta-analysis, however, did observe a decreased complication rate and less surgery. Despite the overall lack of reported benefit, interest in gabexate persists with a recent small study suggesting a benefit by delivering it through a continuous regional arterial infusion [55].

Nafomostat is a relatively new protease inhibitor studied for treating acute pancreatitis. This synthetic protease inhibitor has a broad spectrum of enzyme inhibitory activity that is up to 100 times more potent than gabexate [49]. The design of human clinical studies has been different from aprotinin and gabexate. These studies have included antibiotics, severe acute pancreatitis patients, and delivery of nafomostat by continuous regional arterial infusions (CRAI). This relatively invasive technique delivers a higher concentration of drug through a catheter that is placed into major arterial branches (celiac axis and/or superior mesenteric artery) and must be performed by an interventional radiologist.

Takeda and colleagues first described a clinical trial of 53 patients with severe acute pancreatitis using nafomostat. One group of patients was given peripheral nafomostat and antibiotics (imipenem) intravenously greater than 8 days from symptom onset. The second group was given nafomostat by CRAI with peripherally administered antibiotics to a group that presented less than 7 days from symptom onset. The third group gave both nafomostat and antibiotics by CRAI to a group of patients who presented within 7 days of onset. They reported a progressive mortality benefit from group 1 to 3 (44 % vs. 14 % vs. 7 %) and the development of necrosis (50 % vs. 23 % vs. 0 %) [56]. Takeda and colleagues reported a subsequent study that demonstrated earlier CRAI of nafomostat (<48 h compared to >72 h) was associated with improved mortality (3.2 % vs. 26.3 %) [57]. Imaizumi and colleagues studied 51 patients with severe acute pancreatitis and reported that CRAI compared to non-CRAI delivery of nafomostat and antibiotics was associated with decreased need for surgery and improved mortality [58]. A more recent study of 78 randomized patients between CRAI nafomostat and antibiotic to just antibiotics showed improved mortality (5 % vs. 23 %) and decreased need for surgery [59].

Among the three most studied protease inhibitors (aprotinin, gabexate, and nafomostat), the

most promising outcomes data is associated with nafomostat. However, these studies with nafomostat are relatively small, involve the use of antibiotics, and require a relatively invasive procedure. At this time, none of these medications are accepted as part of standard clinical care for treating severe acute pancreatitis. Further study with nafomostat via CRAI may prove promising.

Immunomodulators

As discussed above, the pathophysiology of acute pancreatitis begins in the acinar cell and if left uncontrolled triggers an immunological cascade that leads to systemic inflammatory response syndrome and sepsis. Consequently, pharmacologic interventions that may mitigate this cascade have been studied for treating severe acute pancreatitis. These include lexipafant, a platelet activation factor inhibitor, and dotrecogin alfa, a genetically engineered activated protein C.

Under physiological conditions, endothelial cells, macrophages, neutrophils, and platelets produce platelet-activating factor (PAF) during the normal course of inflammation leading to platelet aggregation, hypotension, and vascular leak. Preclinical studies of acute pancreatitis have demonstrated a significant role for PAF in the pathophysiology of acute pancreatitis and the use of a PAF blocker to mitigate disease [60, 61]. Lexipafant is a PAF antagonist that has been studied in several clinical trials in humans.

The first clinical trial randomized 83 patients with acute pancreatitis, of whom 29 had severe acute pancreatitis. Lexipafant was administered intravenously on a daily basis (60 mg) for 3 days. While no significant difference in mortality was observed, a significant decrease in organ failure at day 3 in the treatment arm was reported [62]. Another study randomized 50 patients with severe acute pancreatitis with the treatment arm receiving 100 mg daily for 7 days. The treatment group had significantly less organ failure, with a trend toward a reduction in mortality and SIRS [63]. The largest randomized study to date was performed by Johnson and colleagues randomizing 290 patients with severe acute pancreatitis (APACHE > 6) with the treatment group receiving 100 mg daily for 7 days starting within 72 h of symptom onset. No significant difference in organ failure reduction or local complications was observed. The authors concluded that lexipafant alone was not sufficient to ameliorate severe acute pancreatitis [64].

Dotrecogin Alfa is an analogue of endogenous protein C that has demonstrated a mortality benefit in severe sepsis [65]. Endogenous protein C is synthesized in the liver and it inhibits thrombin generation and facilitates thrombolysis. Lower levels of activated protein C are associated with higher mortality in acute pancreatitis. Preclinical studies in acute pancreatitis show improved tissue histology, decreased rates of infection, and lower serum markers of inflammation. Activated protein C may mitigate severe acute pancreatitis by several immunomodulatory mechanisms—regulation of leukocyte endothelial interaction, improved intestinal microcirculation, and regulation of mitogen-activated kinases [66]. The first report of benefit using dotrecogin alfa in acute pancreatitis involved two case reports [67]. A subsequent pilot study of 32 patients with severe acute pancreatitis was studied. These patients received dotrecogin alfa within 96 h of symptom onset. No clinically significant difference in this pilot study was observed [68].

While modulating the immune system in acute pancreatitis as a pharmacological strategy is gaining more interest as knowledge of the pathophysiology unfolds, these recent targets, while promising in preclinical studies, have yet to translate into clinical practice [10].

Antioxidant Agents

Within the last decade, several clinical trials studying the benefit of antioxidant agents for acute pancreatitis have been published. The basis for this involves the recognized role of reactive oxygen species and cellular injury without immediate detoxification. Antioxidant agents that have been studied include a variety of different compounds including *n*-acetylcysteine, methionine, beta-carotene, selenium, ascorbic acid, and

alpha-tocopherol. Preclinical studies in acute pancreatitis demonstrate chemically reduced levels of glutathione and increased levels of oxidized glutathione suggesting a benefit with antioxidant intervention [69].

Three different clinical trials have been recently published on this topic. Siriwardena and colleagues reported a randomized controlled trial of 43 patients with predicted severe acute pancreatitis. The treatment group received intravenous *n*-acteylcysteine, selenium, and vitamin C. They demonstrated that serum levels of antioxidants increased and markers of oxidative stress decreased in the treatment group. The primary outcome was the development of organ dysfunction for which no difference was observed [70]. In another study of 53 patients, the treatment group received vitamin C, *n*-acetylcysteine, and a tablet of multiple antioxidants (antoxyl-forte). No significant difference in length of stay or complications was observed [71]. The final study randomized 39 patients with acute pancreatitis to receive vitamins A, C, and E within 96 h of symptom onset and observed no significant difference in organ dysfunction [72]. While this may be another example of a disconnect between preclinical evidence and clinical studies, it is possible that these studies, being all fairly small, were not powered enough to detect a real difference.

In severe acute pancreatitis, there is significant catabolic stress and active nutrient repletion is associated with a mortality benefit. The use of antioxidants for treating acute pancreatitis falls within an evolving proposed concept of "pharmaconutrition"—that nutrients can provide benefit beyond repletion of a deficiency [73]. Glutamine is a potent antioxidant that plays an important role in enterocyte, lymphocyte, macrophage, and neutrophil development. Consequently, it has been studied as a treatment for acute pancreatitis. Xue and colleagues randomized 80 patients to receive alanyl-glutamine dipeptide intravenously for 10 days starting either on the day of admission or at hospital day 5 (there was no placebo group). Complications, length of stay, need for surgery, and mortality were decreased in the early administration group [74]. Asrani and colleagues performed a meta-analysis of randomized controlled trials of glutamine use for acute pancreatitis. They identified 12 studies of 505 patients with acute pancreatitis. They reported a mortality benefit (RR 0.3; 95 % CI 0.15–0.6), reduced infectious complications (RR 0.58; 95 % CI 0.39–0.87) but no difference in length of stay. Interestingly, the benefit of glutamine use was observed in only patients who received total parenteral nutrition. Patients receiving enteral nutrition did not benefit from additional glutamine supplementation [75].

Anti-inflammatory

Since acute pancreatitis is primarily characterized by a state of acute inflammation leading to cellular injury, anti-inflammatory medications have been studied including indomethacin. The mechanism of action involves inhibition of phospholipase A2 activity, cyclooxygenase activity, and mediation of neutrophil endothelial interactions [76]. Preclinical animal studies have demonstrated a benefit with indomethacin [77]. Human studies, however, have yet to validate a clear benefit with the exception of post-ERCP pancreatitis (PEP). Ebbehoj and colleagues randomized 30 patients with acute pancreatitis with the treatment group receiving 50 mg of rectal indomethacin twice a day. The only outcomes reported were decreased pain and opiate use [78]. Elmunzer and colleagues recently demonstrated in a large multi-center study of 602 patients at high risk for developing PEP that one dose of rectal indomethacin after the procedure reduced the incidence of pancreatitis [79]. While this suggests that indomethacin may have a therapeutic role in preventing acute pancreatitis, there is a lack of clinical data to support its efficacy in patients outside of PEP.

Pharmacologic Therapies for PEP

PEP is a common cause of acute pancreatitis. Fortunately, the vast majority of cases do not evolve into severe disease. Aside from the possibility that the mechanism of PEP is unique

Table 11.3 Summary of pharmacological agents studied in clinical trials for post-ERCP pancreatitis

Pharmacological agent	Study design	Sample size	Post-ERCP pancreatitis rate	Citation
Anti-secretory agents				
Somatostatin	RCT[a]	160	Treatment: 2.7 %, placebo: 10 %[b]	[80]
Somatostatin/diclofenac	RCT	540	Treatment: 4.7 %, placebo: 10.4 %[b]	[81]
IV Octreotide	RCT	202	Treatment: 2 %, placebo: 9 %[b]	[82]
Protease inhibitors				
Nafomostat	RCT	608	Treatment: 5.1 %, placebo: 13 %[b]	[85]
Ulinastatin	RCT	406	Treatment: 2.9 %, placebo: 7.4 %[b]	[84]
Immunomodulators				
IL-10	RCT	137	Treatment: 10 %, placebo: 24 %[b]	[86]
	RCT	305	Treatment: 15 %, placebo: 14 %	[87]
Anti-inflammatory				
Prednisone	RCT	200	Treatment: 12 %, placebo: 7.9 %	[90]
Hydrocortisone	RCT	120	Treatment: 1.6 %, placebo: 11.9 %[b]	[91]
Indomethacin	RCT	602	Treatment: 9.2 %, placebo: 16.9 %[b]	[79]
Antioxidants				
n-Acetylcysteine	RCT	256	Treatment: 12.1 %, placebo: 9.6 %	[92]
Allopurinol	RCT	200	Treatment: 12 %, placebo: 7.9 %	[90]
Smooth muscle relaxant				
Glyceryl nitrate	RCT	806	Treatment: 4.5 %, placebo: 7.1 %	[94]

[a]Randomized controlled trial
[b]Statistically significant

compared to other known etiologies, it has been a popular focus for studying various pharmacological agents for prevention of acute pancreatitis. Since the incidence of pancreatitis episodes can be more easily predicted (i.e., the day of ERCP), clinical trials are relatively easier to perform with the primary outcome being the development of acute pancreatitis. Further, the design of providing a therapy before potentially inducing pancreatitis is more similar to preclinical study designs to suggest more direct translatability. Besides the trial involving rectal indomethacin mentioned above, other pharmacological agents will be briefly reviewed [79].

Active clinical trials in preventing PEP have been ongoing for the past two decades and include many of the pharmacologic agents described above (Table 11.3). These trials tend to be larger because enrollment is more predictable. Among anti-secretory agents, somatostatin with and without diclofenac and octreotide have been studied in randomized controlled trials. Bordas and colleagues randomized 160 patients and found a PEP rate of 10 % in the placebo group compared to 2.5 % in the somatostatin-treated group. In subgroup analysis, this benefit was observed in those patients undergoing sphincterotomy [80]. In a more recent study by Katsinelos and colleagues, somatostatin was added to diclofenac in a randomized study of 540 patients. The overall PEP rate was 7.2 % with the placebo-treated group experiencing a 10.4 % rate compared to the combination-treated group of 4.7 % [81]. It is unclear from this study whether one drug primarily accounts for the benefit. Thomopoulos and colleagues demonstrated a positive benefit with a 24-h infusion with octreotide in a randomized trial of 202 patients [82]. Treated patients had a PEP rate of 2 % compared to 9 % in the placebo group.

Among protease inhibitors, gabexate mesilate, ulinastatin, and nafomostat have been studied in this population [83–85]. Tsujino and colleagues randomized 406 patients to IV infusion with ulinastatin versus placebo before ERCP. The ulinastatin group had a PEP rate of 2.9 % that was significantly lower than 7.4 % in the placebo group [84]. Park and colleagues randomized 608

patients to three different groups: control group, IV nafomostat 20 mg, and IV nafomostat 50 mg before ERCP. While they reported a benefit with nafomostat-treated groups compared to controls, the higher dose did not further protect those patients at high risk for PEP [85].

Among immunomodulators, recombinant IL-10 has been studied with early promise followed by lack of validation in subsequent studies. Deviere and colleagues randomized 144 patients to receive IL-10 infusions compared to placebo with an observed protected effect [86]. A subsequent trial by Sherman and colleagues failed to show a benefit at an interim analysis of 305 randomized patients and terminated the study [87]. Although benefit with the use of non-steroidal anti-inflammatory medications including indomethacin and diclofenac have been observed, the use of steroids have had mixed results [79, 88, 89]. Brudzynska and colleagues randomized 300 patients to prednisone, allopurinol, or placebo before ERCP and found no protective benefit against PEP [90]. In a smaller randomized study of 120 patients, 100 mg of hydrocortisone prior to ERCP reduced PEP from 11.9 % in the placebo group to 1.6 % in the treated group suggesting a significant benefit [91]. Antioxidant therapy with *n*-acetylcysteine and allopurinol has been studied in relatively large randomized trials with no reported protected benefit [90, 92]. Nitroglycerin products to reduce sphincter hypertension have demonstrated benefits in smaller studies without subsequent validation in larger randomized trials [93, 94].

The search for a pharmacological agent for treating human acute pancreatitis has been fairly extensive. The historical arc for most of these agents is one of promise from preclinical studies, followed by a few promising small pilot clinical trials. Most, however, have failed to be validated at larger studies. Meta-analyses have been more positive about various agents, but this may reflect a weighting bias towards smaller and unpublished studies. In PEP, there are more positive clinical trial data for various pharmacological agents. Most, however, have yet to be accepted in standard clinical practice. In non-PEP as well, there is no current pharmacologic agent that has successfully navigated its way into clinical practice [3, 41]. While some of these agents including nafomostat and glutamine may merit further clinical study, the future may lie in novel agents.

Future Targets: Opportunities for Therapeutic Development

Despite previous efforts, there are promising opportunities for therapeutic development. Specifically, strategies that target and alter the activities of key immune cells may provide potential therapeutic benefit as demonstrated in preclinical studies. In acute pancreatitis, macrophages can play both a pro-inflammatory and anti-inflammatory role. Various modifiers such as IL-4 and IL-13 have demonstrated capacity to convert pancreatitis-activated macrophages (M1) into reparative macrophages (M2). Hemin-activated macrophages express high levels of hemoxygenase-1 (HO-1) that in turn promotes production of anti-inflammatory agents including carbon monoxide and biliverdin. These agents induce IL-10, IL-22, and p38 MAPK. Introduction of hemin-activated macrophages protects against experimental pancreatitis [10, 95]. In humans, HO-1 levels are upregulated in acute pancreatitis and that ex vivo treatment of patient blood with Panhematin, an FDA-approved medication for acute intermittent porphyria, can prime HO-1 production [96]. Habtezion and colleagues have shown that Panhematin given before experimental pancreatitis upregulates hemin-activated macrophages and leads to less pancreatic injury. More importantly, they have shown in their experimental model that if given after pancreatitis develops, in both early and late stages of disease, Panhematin treatment ameliorates the extent of pancreatitis-related injury [97].

Another perhaps underappreciated immune-related target involves the kallikrein-kinin and complement systems. As mentioned above, severe acute pancreatitis is associated with elevated C3a and sC5-9 levels [13]. The C1 esterase inhibitor (C1 INH) physiologically inhibits a variety of plasma proteolytic enzymes including the activated C1 complex and kallikrein [98].

In experimental models of acute pancreatitis, C1 INH given before the onset of pancreatitis demonstrated a potential protective benefit [99]. In particular, C1-INH may have a protective benefit in severe acute pancreatitis [100]. In small human studies, the use of C1-INH concentrate has demonstrated some protective benefit in acute pancreatitis [101, 102]. Pharmacological targets of the complement system have already been developed in other diseases that may have utility in acute pancreatitis. One example includes recombinant C1-INH that is currently available in Europe for the treatment of hereditary angioedema [103]. Another example is eculizumab, which is a monoclonal antibody that binds with high affinity to complement protein C5 preventing generation of the terminal complement complex C5b-9. It is currently approved for treating paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome [104].

Some potentially novel pharmacologic agents are being studied in PEP given some of the advantages in clinical trial design. Fluhr and colleagues recently published their design for a randomized controlled trial of IV magnesium to prevent PEP. Intra-cellular calcium release plays an important role in initiating protease activation. Magnesium is a calcium antagonist and counteracts calcium signaling. This study intends to randomize 502 patients to IV magnesium 60 min before and 6 h after ERCP or placebo [105].

Conclusion

Although there have been some positive studies of various pharmacological agents, the vast majority have failed to demonstrate a consistent benefit in large validation studies such that there is no current drug recognized for use in clinical practice for treating acute pancreatitis. Perhaps, one of the major reasons for this relates to differences between promising preclinical studies in experimental pancreatitis and human clinical trials. Besides the question of whether these models accurately reflect human disease, most preclinical studies administer the medication prior to pancreatic injury such that the medication in question provides a protective effect. In the clinical situation, the drug of interest is tested when the injury has already occurred and the inflammatory cascade associated with pancreatitis has begun.

With some drugs including nafomostat and glutamine requiring further validation and potential novel drugs to be tested hopefully soon, the design of future clinical trials needs to be reconsidered. Going forward, we need to design clinical trials that administer treatment within 24 h (or as soon as possible) from symptom onset. Even earlier delivery may be key (i.e., within 4 h of arriving into the ER), akin to treatment of ST-elevation myocardial infarctions where time to catheterization is now part of clinical practice. This will maximize any candidate drug's potential to interrupt the inflammatory cascade and injury. A continued focus of trials on predicted severe disease will more likely identify a candidate treatment, as trials that include patients with mild pancreatitis require larger sample sizes to detect a meaningful difference. To minimize heterogeneity, clinical trials should also standardize eligibility, supportive treatment approaches, and outcomes. Eligibility for severe disease as well as clinically relevant outcomes should adopt standards set forth by the revised Atlanta classification [2]. Clinically meaningful primary outcomes primarily include mortality, the development and resolution of organ failure, SIRS, sterile and infected necrosis, and other local complications. Important secondary outcomes include the length of stay, the amount of pain medication required, quality of life, and cost of care.

Despite past shortcomings of studied pharmacological agents, there remains promise in discovering and developing an effective pharmacological therapy for acute pancreatitis. The lessons learned from past clinical trials along with increased understanding of the immune system in this disease provide meaningful direction for substantial progress. When, not if, such a discovery occurs, it will fundamentally change our current management paradigm from one of supportive therapy to abortive therapy.

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