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Juliana Hey-Hadavi, Prasad Velisetty & Swapnali Mhatre

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REVIEW

Trends and recent developments in pharmacotherapy of acute pancreatitis

Juliana Hey-Hadavi[a], Prasad Velisetty[b] and Swapnali Mhatre[c]

[a]Pfizer Inc, Brooklyn, NY, USA; [b]Pfizer UK, Walton on Oaks, UK; [c]Pfizer India, Mumbai, India

ABSTRACT

Acute pancreatitis (AP), a complex inflammatory disease of the pancreas, is associated with increased morbidity and mortality. Currently, no specific therapies are approved for its treatment, and management is primarily based on supportive care. Despite enhanced understanding of AP pathogenesis, patients remain at significant risk owing to a lack of targeted drug treatments. Therefore, there is an urgent need for effective pharmacological therapeutic measures which may inhibit the early systemic inflammation, thereby preventing subsequent organ failure. This narrative review summarizes the available treatment options for AP and highlights the potential drug classes and pharmacologic therapies including those under clinical development. Although, several therapies targeting different aspects of AP pathogenesis have been investigated, some therapies with promising preclinical activity have been rendered ineffective in clinical trials. Other novel drug classes or molecules including dabigatran (anticoagulant), ulinastatin (protease inhibitor), infliximab (monoclonal antibody), spautin-A41 (autophagy inhibitor), and CM4620-Injectible Emulsion (calcium channel inhibitor) await further clinical assessment. Alternative treatment options using stem cells and nanoparticles are also being explored and may hold promise for AP therapy. However, challenges for exploring targeted treatment approaches include disease complexity, timing of therapeutic intervention, and establishing appropriate clinical endpoints. Understanding the role of specific biomarkers may help in identifying appropriate targets for drug discovery and facilitate determining relevant clinical study endpoints to monitor disease severity and progression, thereby aiding in design of more precise therapies with improved clinical outcomes.

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1. Introduction

Acute pancreatitis (AP) is characterized by severe abdominal pain usually accompanied with elevated pancreatic enzymes owing to inflammation in the pancreas [1]. Notably, severe forms of AP are associated with considerable mortality, due to systemic inflammatory response syndrome (SIRS), sepsis, or multiorgan failure [2,3]. Despite a reduction in the case fatality being observed over time, the population mortality has remained largely unchanged [4]. While the overall mortality due to AP is estimated to be 5%, the mortality in severe acute pancreatitis (SAP) can be as high as 25% [5]. Alcohol, gallstones, and hypertriglyceridemia (HTG) are predominant etiological factors for AP [6]. Worldwide, the etiologic pattern of AP varies according to the geographical region. In Europe and North America, gallstones (50%) and alcohol (25%) are most prevalent. Other factors including drugs (valproate, steroids, azathioprine), HTG or lipoprotein lipase deficiency, endoscopic retrograde cholangiopancreatography, hypercalcemia, pancreas divisum, and viral infections (mumps, coxsackie B4) constitute as rare causes (<5%), while idiopathic pancreatitis account for about 10% of cases [7].

According to the Global Burden of Disease Study 2019, a total of 2,814,972.3 cases of AP were reported in 2019, which was higher than 1990 by 62.9% [8]. The global estimates of AP incidence were reported to be 33.74 cases (95% CI 23 · 33–48 · 81) per 100,000 patient-years, and that for mortality was 1.60 deaths (95% CI 0 · 85–1 · 58) per 100,000 patient-years [9]. A study from the United States (U.S.) revealed a significant increasing trend in the overall rate of hospitalizations due to AP from 65.38 per 100,000 US adults in 2011 to 81.88 per 100,000 US adults in 2014 [10]. In Europe, the incidence of AP ranged from 4.6 to 100 per 100,000 population across 17 countries [11]. A prospective, multicenter study revealed that AP patients with organ failure alone had significantly higher mortality as compared to those with organ failure and infected pancreatic necrosis (44% vs 29%, P = 0.04) [12]. Of note, recent studies have also reported cases of AP in patients with coronavirus disease 2019 (COVID-19) [13,14] with a positive correlation between AP and COVID-19 pneumonia [15]. However, current evidence does not establish any link between the two conditions and this needs further investigation [16].

With the current disease burden of AP and mortality risk associated with SAP, there is an urgent need for targeted novel treatment strategies that halt disease progression and improve patient outcomes. The current review will focus on the treatment landscape of AP and summarize recent clinical evidence on potential pharmacotherapy approaches identified for AP, including drug classes or inhibitors under clinical development. This review will further discuss the limitations of applied approaches, potential therapeutic implications, and scope for future treatment modalities for managing AP.

CONTACT Juliana Hey-Hadavi Judith.h.hadavi@pfizer.com Pfizer Inc, Brooklyn, 235 E 42nd Street New York, NY 10017, USA

2. Pathophysiology

Understanding of the pathophysiology of AP offers a great foundation to explore future therapies. Several recent studies have suggested that AP evolves in three phases. The initial phase is characterized by intrapancreatic digestive enzyme activation such as trypsin, and acinar cell injury. Trypsin activation appears to be mediated by lysosomal hydrolases such as cathepsin B that become colocalized with digestive enzymes in intracellular organelles. It is currently believed that acinar cell injury is the consequence of trypsin activation [17].

The second phase is marked by the activation, chemoattraction, and sequestration of leukocytes and macrophages in the pancreas, which results in an enhanced inflammatory reaction [17]. Neutrophils also play a pivotal role in mediating pancreatic tissue injury and inflammation [18]. Preclinical data have indicated that the severity of AP was ameliorated with neutrophil depletion induced by prior administration of an antineutrophil serum [19,20]. Activation of trypsinogen potentially drives neutrophil infiltration in the pancreas during the onset of AP, and the activated neutrophils further regulate trypsinogen activation [18]. Interestingly, as reported by Abdulla et al. [19], intrapancreatic acinar cell activation of trypsinogen is a dynamic process involving an early neutrophil-independent and a late neutrophil-dependent phase. Several studies have also implicated a role for platelet-activating factor (PAF) in the systemic inflammatory process of AP [21,22]. As demonstrated by Wang et al. [23], serum platelet index such as platelet distribution width (PDW) may serve as a potential prognostic factor for persistent organ failure (POF) in acute pancreatitis, with a higher serum PDW value on admission observed for patients at risk of POF.

The third phase of AP is characterized by extrapancreatic inflammation. Sequestration of activated granulocytes and macrophages to the pancreas is triggered by the local release of cytokines. The immune cells also release cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and IL-6 which activate Kupffer cells in the liver, thereby elevating cytokine levels in the blood. This causes distant organ damage including SIRS, acute respiratory distress syndrome, or multiorgan failure [17]. Activated proteolytic enzymes, especially trypsin also activates other enzymes including elastase and phospholipase. The active enzymes and cytokines then digest cellular membranes and cause proteolysis, edema, interstitial hemorrhage, vascular damage, fat necrosis, and parenchymal cell necrosis [17,24].

Intracellular activation of pancreatic proenzymes leads to the destruction of the parenchyma and autodigestion of the pancreas [25,26]. Recent reports have suggested that impairment in autophagy due to lysosomal dysfunction may play a role in AP, leading to accumulation of vacuoles and trypsin in acinar cells, thereby causing necrosis and inflammation [27,28]. Studies have also highlighted the role of NF-κB, the ubiquitous nuclear transcription factor that possibly regulates the early stages of AP by mediating the expression of numerous genes involved in inflammation [29,30]. NF-κB is activated following pancreatic acinar cell injury and drives the release of cytokines from the pancreas and circulating immune cells. These cytokines further stimulate the activation of NF-κB in surrounding immune cells, thereby triggering systemic inflammation [31].

Genetic mutations also play an important role in pathogenesis of AP. Mutations in the genes including cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2), serine protease inhibitor Kazal type 1 (SPINK1), cystic fibrosis transmembrane conductance regulator (CFTR), chymotrypsinogen C (CTRC), and calcium-sensing receptor (CASR) have been associated with increased risk of AP. These genetic factors may prevent activation of trypsinogen or block active trypsin in the pancreas and therefore, influence the development of AP [32]. Studies have identified presence of these mutated genes in patients with AP [33,34]. Further evaluation may help explore the role of these genetic mutations on the disease pathogenesis and/or severity.

3. Current management of acute pancreatitis

Disease classification based on severity (mild, moderate, and severe) is a crucial determinant for the management of AP. This enables the treating physicians to identify and stratify the severity of the disease and decide the course of therapy to avoid further complications.

According to the revised Atlanta classification, AP can be divided into two broad categories: acute inflammation without necrosis (interstitial edematous pancreatitis) and necrotizing pancreatitis [35,36]. While a majority of patients are affected with mild AP, moderate or severe pancreatitis accounts for around 20% of cases [37]. The classification of AP based upon severity is summarized in Table 1.

Due to the unavailability of pharmacologic therapies, the treatment of AP is primarily supportive. Several enhancements were attempted for the constituents of supportive therapy; however, to date, there are no approved treatments to suppress the powerful cascade of inflammatory factors associated with AP [38]. With this limitation, most clinical management guidelines emphasize using an approach that includes predicting and establishing the severity of AP to triage patients to appropriate levels of care. These include administering supportive care with intravenous (IV) fluid resuscitation and enteral nutrition and treating the underlying cause and complications by appropriate use of urgent endoscopic retrograde cholangiopancreatography, early cholecystectomy,

Table 1. Classification of Acute pancreatitis – revised Atlanta classification [32,33].

Disease severity	Clinical features
Mild AP	No organ failure, no local or systemic complications, rare mortality
Moderately severe AP	Organ failure that resolves within 48 h and/or, local or systemic complications without persistent organ failure, less mortality
Severe AP	Persistent organ failure (>48 h; single, multiple organ failure), high mortality

AP, acute pancreatitis.

targeted use of antibiotics, and interventions for pancreatic fluid collections in the later stages (usually after 4 weeks) [39,40].

3.1 Fluid resuscitation

Ringer's lactate is recommended for initial fluid resuscitation in AP. Goal-directed IV fluid therapy with initial use of 5–10 ml/kg/h fluid is employed until resuscitation goals are achieved [41]. The preferred approach to assess the response to fluid resuscitation is based on one or more of the following: 1) fluid resuscitation response can be either as noninvasive clinical targets of heart rate <120/min, mean arterial pressure between 65 and 85 mmHg, and urinary output >0.5 to 1 mL; 2) invasive clinical targets of stroke volume variation, and intrathoracic blood volume determination; and 3) biochemical targets of hematocrit 35%–44% [40]. Importantly, early aggressive IV hydration should be provided to all patients except for those with cardiovascular and/or renal comorbidities [39].

3.2 Analgesics

Abdominal pain is often a predominant symptom in patients with AP and is generally treated with non-steroid anti-inflammatory drugs (NSAIDs) and opioids such as buprenorphine, pethidine, pentazocine, fentanyl, and morphine [42,43]. Pain management is usually based on the WHO analgesic ladder which consists of 4 steps (Step 1: NSAID, Step 2: low potent opioid ± NSAID ± adjuvant drugs, Step 3: High potent opioid ± NSAID ± adjuvant drugs, Step 4: interventional treatment ± high potent opioid ± NSAID ± adjuvant drugs) [42].

3.3 Nutrition

Patients with AP are at significant risk of malnutrition, thereby requiring nutritional support for therapy management [44]. As per the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, patients with mild AP are recommended a low-fat oral diet as these patients can tolerate early oral feeding, and this involves a shorter length of stay (LOS) compared with conventional oral feeding (introduced after enzyme decrease, pain resolution, and bowel movement). Moreover, enteral nutrition (EN) should be preferred to parenteral nutrition (PN), considering EN is well tolerated compared to PN and associated with reduced complications, multi-organ failure, and mortality. In patients intolerant to oral feeding, EN should be started within 24–72 h of admission, constituting a standard polymeric diet. EN should be administered via a nasogastric tube and in case of digestive intolerance, administration via a nasojejunal tube should be preferred [44].

3.4 Antibiotics

Studies have identified that infectious complications such as bacteremia, urinary tract infections, and pneumonia increase the risk of mortality in patients with AP [45,46]. Moreover, such infections occur during the initial days of admission, thus requiring early treatment. Studies have also highlighted that extrapancreatic infections are associated with increased mortality [45]. Therefore, antibiotics should be started in case of suspected infection while the source of the infection is still being determined. However, antibiotics should be discontinued in case of negative cultures and no identifiable source of infection [47].

4. Potential treatment approaches for AP

The following sections summarize the potential drug classes and pharmacologic therapies developed and/or under clinical development for specific pharmacologic management of AP. Additionally, the clinical trial overview of potential therapeutic agents is listed in Table 2.

4.1. Antioxidants

Oxidative stress may play a key role in inflammatory conditions such as AP [48]. Therefore, supplementation with antioxidants has been explored as a potential therapeutic measure for AP treatment.

4.1.1. Apigenin

Apigenin (4,5,7 trihydroxy flavone) is derived from plants and possesses anti-inflammatory, antioxidant, anti-allergic, anti-osteoporotic, and anti-cancerous activities [49,50]. A study on an experimental model of pancreatitis in Wistar rats reported that oral administration of apigenin ameliorated all pathologic parameters of inflammation and reduced myeloperoxidase activity [50]. Another study on an experimental model of AP demonstrated the anti-inflammatory effect of apigenin treatment with significantly reduced TNF-α levels and prevention of pancreatic necrosis compared to the control group, thereby supporting the role of apigenin as an adjunct therapy [51]. Future clinical studies are warranted to ascertain the clinical application of apigenin as an adjunct to an effective therapeutic strategy.

4.1.2. Glycyrrhizin

Glycyrrhizinic acid or glycyrrhizin (GL) is a natural sweetener derived from plants. An experimental study on taurocholate-induced AP in rats demonstrated the anti-inflammatory and antioxidant effects of GL treatment which significantly decreased pancreatic tissue myeloperoxidase activities and tissue malondialdehyde (MDA) levels compared to the control groups. Histopathology analysis also revealed a significant reduction in acinar cell necrosis, hemorrhage, and edema in the treatment group [52]. Another preclinical study also reported decreased levels of serum TNF-α and IL-6 as well as downregulation of the High Mobility Group Box-1 protein following administration of GL which improved pancreatic lesions in the experimental model for AP [53].

4.1.3. Vitamin C

Vitamin C is a key antioxidant found in human blood plasma. A study comparing the concentrations of vitamin C and its bioavailable form, ascorbic acid between healthy volunteers and patients with AP revealed very low levels of vitamin C and

Table 2. Summary of clinical trials on new treatment approaches.

Pharmacologic molecule/inhibitor	Class	Study Phase/Design (Study status)	Indication	Comparator	ClinicalTrials.gov Identifier[a]
CM4620	Calcium channel blocker	Phase 2/Open-Label, Dose-Response Study (Completed)	Severe acute pancreatitis	None	NCT03401190
		Phase 1/2/Open label (Ongoing)		None	NCT04195347
CM-4620 Injectable Emulsion (CM4620- IE)	Calcium channel blocker	Phase 2/Open label PK/PD Study (Completed)	Severe acute pancreatitis	None	NCT03709342
		Phase 2/Randomized, Double-Blind, Placebo-controlled Dose-Ranging Study (Ongoing)		Placebo	NCT04681066
Dabigatran	Anticoagulant	Phase 1/Randomized Study (Ongoing)	Acute pancreatitis	Standard of care	NCT03807856
Hydrocortisone	Corticosteroid	Phase 2/Randomized, Placebo controlled, Double-blind (Not yet recruiting)	Acute pancreatitis	Placebo	NCT05160506
Infliximab	TNF-α inhibitor	Phase 2b/ Randomized, Placebo-controlled, Double-blind (Suspended due to COVID-19)	Acute pancreatitis	Placebo	NCT03684278
Omega-3 Fish Oil	Omega-3 Fish Oil (lipid emulsion)	Phase 2/Randomized/Parallel Assignment (Completed)	Severe acute pancreatitis	Placebo	NCT01745861
Pentoxifylline	TNF-α blocker	Phase 1/ Randomized, Double-Blind Placebo-controlled Study (Completed)	Acute pancreatitis	Placebo	NCT01292005
		Phase 3/Double-Blind Placebo-controlled Randomized Trial (Completed)		Placebo	NCT02487225
SCM-AGH	Allogeneic human bone marrow derived mesenchymal stem cells	Phase I Open-label, Single Arm /3 + 3 design Phase II Randomized, Double-blind, 2-arm, Placebo-controlled, Parallel arm (Ongoing)	Severe acute pancreatitis	Placebo	NCT04189419
Simvastatin	HMG-CoA reductase inhibitor	Phase 3/Triple Blind, Randomized Controlled Trial (Ongoing)	Relapsing pancreatitis	Placebo	NCT04021498
Ulinastatin	Serine Protease inhibitor	Phase 4/Randomized Study (Suspended due to project revision; may start again)	Severe acute pancreatitis	Placebo	NCT01132521

[a]Clinical trial information is available on ClinicalTrials.gov.

ascorbic acid in patients, thereby suggesting parenteral administration of vitamin C and ascorbic acid as a possible means for treatment in these patients [54]. Another double-blind, placebo-controlled, randomized trial was conducted in patients with SAP using IV antioxidants N-acetylcysteine, selenium, and vitamin C. The primary endpoint of organ dysfunction was not significantly different between the antioxidant and placebo groups, and a trend toward more organ dysfunction was observed in the antioxidant group. Given these observations, the authors cautioned against considering antioxidant treatment in patients with SAP [55]. Thus, current evidence supporting clinical benefits of vitamin C in AP remains inconclusive, and high-quality studies in future are required for further analysis.

4.1.4. Glutamine

Glutamine is the most abundant free amino acid that regulates several crucial biological functions. Depletion of plasma glutamine occurs in critically ill patients and has been associated with increased ICU mortality. In a randomized controlled trial, the effect of enteral glutamine supplementation on clinical outcomes, gut permeability, systemic inflammation, oxidative stress, and plasma glutamine levels was evaluated in patients with severe and predicted severe AP. No significant improvement was observed in the development of infected necrosis and in-hospital mortality between the groups. However, enteral glutamine supplementation demonstrated improvement in gut permeability, oxidative stress, and a trend toward improvement in organ function as depicted by the Modified Marshall score [56]. A recently published meta-analysis indicated beneficial effects of glutamine supplementation in patients with AP with significantly reduced infectious complications and hospital stay, albeit with a non-significant decrease in mortality [57].

According to the recent ESPEN recommendations, there is no role for immuno-nutrition (parenteral glutamine) in SAP. However, when EN is not feasible or contraindicated and PN is indicated, parenteral glutamine should be supplemented at 0.20 g/kg per day of L-glutamine [44].

4.2. Anticoagulants

Coagulation and inflammatory processes are interrelated and may be associated with early pathologic events in AP [58].

4.2.1. Heparin

Low molecular weight heparin (LMWH) possesses antithrombin and anti-inflammatory activity [59]. Heparin reduces the microthrombi formation and improves the microcirculation of the pancreas [60]. Heparin administration downregulates TNF-α-induced leukocyte rolling [59] and blocks leukocyte adhesion by inhibiting the interactions between expressed adhesion molecules and endothelial cells [61]. Moreover, heparin also reduces cathepsin G-induced platelet activation by blocking protease activity [62]. Importantly, administration of LMWH in patients with moderately severe and severe AP significantly reduced local and systemic complications with no hemorrhagic complications. However, no significant difference was observed in mortality between the treatment and control groups [60]. A recent meta-analysis of 16 randomized-controlled trials (RCTs) reported that LMWH treatment improved the outcomes in patients with SAP by significantly reducing hospital stay, mortality, incidences of multiple organ failure, pancreatic pseudocyst, and operation rate. Additionally, the LMWH treatment group had lower white blood cells and C-reactive protein levels than the conventional treatment group (control), thereby highlighting the potential benefits for patients with SAP [63].

4.2.2. Activated Protein C

Activated protein C (APC) is an endogenous anticoagulant with antithrombotic, fibrinolytic, and anti-inflammatory properties. However, in a placebo-controlled study conducted in patients with SAP, APC treatment did not improve pivotal coagulation parameters and slowed down recovery from coagulopathy in these patients [64].

4.2.3. Dabigatran

Another anticoagulant dabigatran is an effective inhibitor of trypsin which is activated during pancreatitis in the early phase [65]. An open-label, randomized, pilot study (NCT03807856) on the safety and efficacy of 150 mg dabigatran (BID) for the treatment of AP is currently ongoing (estimated completion in August 2022) [66].

4.3. Protease inhibitors

Protease inhibitors can block premature trypsin activation, the key event in the early pathogenesis of AP, and therefore various protease inhibitors are attractive therapy options for AP.

4.3.1. Ulinastatin

Ulinastatin, an intrinsic trypsin inhibitor derived from the urine of healthy adults has been studied in the management of SAP, mainly in Japan, India, and China [67,68]. However, clinical evidence evaluating the use of ulinastatin in patients with AP, especially those with organ dysfunction(s) is limited. A retrospective analysis assessed patients diagnosed with moderately severe or severe AP and admitted to the ICU with at least one organ dysfunction. The study demonstrated that ulinastatin treatment was associated with improved outcomes in patients with SAP, including lower in-hospital mortality, less incidence of new-onset organ dysfunction, and higher incidence of resolution of existing organ dysfunction within 5 days in comparison with the control group [68]. Another retrospective study evaluated the efficacy of different doses of ulinastatin (200,000; 400,000; and 600,000 IU) for the treatment of SAP. Interestingly, WBC count and mortality rates reduced significantly in the 400,000 and 600,000 IU treatment groups, and a significantly shorter abdominal pain relief time was observed for the 400,000 IU group as compared to the 200,000 IU group. These findings suggested varying efficacy outcomes with different doses of ulinastatin [69]. Of note, a recent study illustrated the underlying mechanism for the effect of ulinastatin in an SAP rat model with ulinastatin administration upregulating the proportion of Tregs in CD4 + T cells. Expression of IL-10, Foxp3, and CTLA-4 were increased in a dose-dependent manner, while levels of IL-1β

and TNF-α, and MPO activity were down-regulated [70]. A combination of ulinastatin and another trypsin inhibitor, somatostatin has also been used to treat SAP. Li C, et al. [71] conducted a randomized controlled study to explore the clinical efficacy of ulinastatin combined with somatostatin for treating SAP. A total of 82 patients were treated with routine therapy with or without ulinastatin combined with somatostatin. This study indicated that ulinastatin combined with somatostatin was effective in patients with SAP by improving intestinal function recovery, treatment efficiency, body immunity, complication rates, and rehabilitation process [71]. Another study on ulinastatin treatment combined with somatostatin demonstrated improved clinical outcomes in patients with SAP. The levels of serum IL-8, CRP, and TNF-α, as well as vascular endothelial function-related factors [NO, von Willebrand factor (vWF), endothelin (ET-1), and CD8+] were lower in the ulinastatin/somatostatin group than the control group (only somatostatin, CG). CD4+ and CD4+/CD8+ levels were higher than those in the control group, whereas recovery times of gastrointestinal function and serum amylase, as well as and hospital stays were shorter in the ulinastatin/somatostatin group than those in CG [72].

4.3.2. Gabexate

Gabexate is a synthetic serine protease inhibitor, reported to improve the microcirculatory environment in acute experimental pancreatitis model in rats [73]. Moreover, gabexate is also known to regulate inflammatory cytokines [67]. In a prospective and double-blind study, the efficacy of somatostatin with or without ulinastatin and gabexate for the treatment of SAP was evaluated. Inflammatory cytokines including TNFα, IL-6, and IL-8 levels decreased significantly and immunosuppressive cytokine IL-10 levels increased significantly after the treatment with somatostatin, ulinastatin, and/or gabexate compared with somatostatin alone. In contrast, significant decrease in frequency of MODS, mortality, and complication was observed only in the somatostatin, ulinastatin, and/or gabexate as compared with somatostatin alone. There were no statistical differences between somatostatin and gabexate compared with somatostatin alone, and between somatostatin, ulinastatin, and gabexate compared with somatostatin and ulinastatin. Thus, gabexate could alleviate clinical symptoms and shorten the course of the disease, however, could not improve the effective ratio or decrease MODS, mortality, and complication [74].

4.4. Anti-secretory agents

Acute pancreatitis is characterized by pancreatic and peripancreatic fat injury, which is partly facilitated by autodigestive enzymes. Therefore, anti-secretory agents can serve as potential therapies for AP considering that excessive stimulation of the exocrine pancreas worsens symptoms of AP [75].

4.4.1. Somatostatin and Octreotide

Somatostatin is an inhibitory peptide hormone with numerous effects on gastrointestinal motility and exocrine pancreas secretions [76] but is limited by its short half-life (2–3 minutes) [77]. Octreotide, a synthetic version of somatostatin with a comparatively longer half-life (approximately 1.7–1.9 hours) was explored as a possible treatment option for AP [76,78]. Overall, neither somatostatin nor octreotide is effective in the treatment of AP [79,80].

4.5. Anti-inflammatory and immunomodulators

The imbalance of inflammatory response can lead to severe disease or even death in patients with AP. Immunomodulation is necessitated to improve the prognosis of patients with SAP which involves SIRS and compensatory anti-inflammatory response syndrome. Therefore, both anti-inflammatory and immune-potentiator drugs are required for the treatment of SAP [81].

4.5.1. Lexipafant

Lexipafant is a PAF receptor antagonist introduced for the treatment of AP. The efficacy of lexipafant was rigorously tested in a double-blind, placebo-controlled, multicenter, Phase 3 study. There was a high frequency of organ failure within 72 hours of the onset of symptoms and consequently, the study could not achieve its primary endpoint i.e. reduction in the frequency of organ failure. Thus, lexipafant treatment failed to reduce new organ failure [82].

4.5.2. Pentoxifylline

Pentoxifylline, a competitive nonselective phosphodiesterase inhibitor is known to reduce inflammation through TNF-α inhibition. However, data on clinical benefit in AP in humans is rather limited. Vege et al. [83] performed a randomized, placebo-controlled study in 28 patients with predicted SAP (pSAP) within 72 hours of diagnosis. The median length of hospitalization and prolonged hospital stay (>4 days) was significantly less frequent in the pentoxifylline group than in the control group. Intensive care unit transfer was none in the pentoxifylline group and 4 in the control group. Patients receiving pentoxifylline had no adverse effects and were considered safe within 72 hours of pSAP [83]. Interestingly, another single center, randomized, double-blind placebo-controlled trial conducted in patients with AP (n = 84) revealed that pentoxifylline did not demonstrate superiority over placebo [84].

4.5.3. Infliximab

Infliximab, a chimeric monoclonal antibody biologic drug is used for the treatment of autoimmune diseases as it blocks the TNF-α activity. Currently, a double-blind, placebo-controlled, multicenter RCT (NCT03684278: RAPID-I trial) designed to evaluate the effectiveness and safety of early infliximab initiation in the treatment of AP in adults is ongoing. Infliximab is administered via IV infusion and will ensure rapid bioavailability to treat AP [85]. RAPID-I may serve as an innovative model for personalized medicine approaches for AP trials in the future [86].

4.5.4. Stem cells

Mesenchymal stem cells (MSCs) are adult stem cells that possess immunomodulatory properties apart from their differentiating abilities and therefore are being evaluated as a new therapeutic approach for AP [87]. An experimental study by Qian et al. [88] revealed that bone-marrow-derived MSCs were able to repair SAP and promote regeneration of necrotized pancreatic tissue by releasing microRNA-9, a key paracrine factor, and inhibiting the NF-κB signaling. Currently, a multicenter, randomized, double-blind, placebo-controlled trial in patients with moderate to severe AP is ongoing in Korea. The trial aims to evaluate the efficacy and safety of IV infusion of allogeneic human bone-marrow-derived mesenchymal stem cells once a day for 3 days and has an estimated completion date in June 2022 [89].

4.6. Other therapies

4.6.1. Nanomedicine

Nanomedicine is an emerging field that employs nanoparticles as targeted and controlled drug delivery vehicles and is being widely used in therapeutics. Nanoparticles serve as potential drug delivery systems due to their small size and unique chemical and biophysical properties including biocompatibility and biodegradability [90]. In an experimental model of AP, bilirubin encapsulated silk fibrin nanoparticles (BRSNPs) reduced oxidative damage and inflammation by inhibiting NF-κB regulated pro-inflammatory signaling as well as activating cytoprotective redox transcription factor, nuclear factor erythroid 2-related factor 2 [91]. Another experimental study demonstrated that yttrium oxide nanoparticles exerted anti-inflammatory effects and attenuated the severity of AP in mice [92]. Thus, exploring the role of nanomedicine for the treatment of AP may be of clinical interest and warrants further evaluation.

4.6.2. Calcium channel inhibitors

Excessive Ca^{2+} influx in acinar cells leads to activation of trypsinogen and plays a pivotal role in cellular injury and the progression of AP [93,94]. CM4620 is a selective small-molecule inhibitor of the Orai1 calcium channel. A recent study demonstrated that CM4620 administration in rats significantly decreased pancreatic edema, acinar cell vacuolization, intrapancreatic trypsin activity, cell death signaling, and acinar cell death. Myeloperoxidase activity and inflammatory cytokine expression in the pancreas and lungs were also reduced [94]. Auxora™, the CM4620 injectable emulsion (CM4620-IE) developed by CalciMedica Inc. demonstrated a favorable safety profile in phase 2, open-label, dose-response study (NCT03401190) in patients with AP and accompanying SIRS. Auxora treatment led to less persistent SIRS, reduced hospitalization, and improved tolerability to solid food as compared to SOC, thereby suggesting a potential treatment option for AP patients with SIRS. These positive results encourage its further clinical development in a larger study [95,96]. Another phase 2, randomized, double-blind, placebo-controlled trial (NCT04681066) is currently ongoing for Auxora in patients with AP and accompanying SIRS. The primary outcome for this trial is time to solid food tolerance and its completion is estimated in October 2022 [97]. Currently, a phase 1/2, open-label, clinical trial (NCT04195347) is ongoing that will assess the tolerability and efficacy of CM4620 in children and young adults with AP caused by asparaginase. The primary objectives of this trial include determining dose-limiting toxicities and the effect on necrotizing pancreatitis in children. The study is estimated to be completed in December 2023 [98].

4.6.3. Autophagy inhibitor

Autophagy plays a crucial role in the development of AP and autophagosome accumulation due to autophagy blockage may be responsible for zymogen activation [99]. Pharmacological inhibition of the autophagy process offers a potential therapeutic strategy for AP [100]. A preclinical study on the spautin-1, a potent autophagy inhibitor demonstrated that trypsin activity significantly decreased following treatment and downregulated serum TNF-α and phosphorylated p65 (subunit of NF-κB) levels in the pancreas. Spautin-1 treatment also alleviated edema, necrosis, and inflammation in pancreatic tissues [99]. A derivative of spautin-1, spautin-A41 is a novel autophagy inhibitor with higher stability and inhibition potency. A preclinical study in mice revealed that spautin-A41 treatment effectively reduced the expression of Class III phosphatidylinositol 3 kinase complexes which is a key complex involved in the initiation and maturation of autophagosomes, and subsequently ameliorated AP [100].

4.6.4. Corticosteroids

Corticosteroids have also been studied as a treatment option for AP. A meta-analysis of six RCTs evaluating the benefits of corticosteroids in patients with SAP reported that corticosteroids treatment was associated with reduction in the length of hospital stay, the need for surgical intervention, and mortality rate [101]. A retrospective study assessing the effect of glucocorticoids in patients with AP also revealed a shorter length of hospital stay and costs with glucocorticoids treatment compared to non-glucocorticoids. In addition, glucocorticoid administration during the early stage of AP did not increase the risk of infection or gastrointestinal bleeding and facilitated fluid resuscitation and reduced mortality in this study [102]. However, further evaluation of these drugs for the treatment of AP may be necessary based on evidence of corticosteroid-induced AP presented in some case reports [103,104]. A phase 2, randomized, double-blind, placebo-controlled trial (NCT05160506) assessing the effect of intravenous hydrocortisone therapy in patients with SAP is currently ongoing (estimated completion in April 2027) [105].

4.6.5. Proton-pump inhibitors

Proton-pump inhibitors (PPIs) have been widely used as therapeutic approach for AP. However, clinical evidence on treatment potential of PPIs still remains inconclusive. Demcsák et al. reported that PPIs did not demonstrate any clinical benefits related to mortality or prevention of gastrointestinal bleeding in patients with AP [106]. Another retrospective, multi-center study evaluating effects of PPIs in patients with AP reported no significant difference in mortality and hospital

stay between the treatment and control (not treated with PPIs) groups. However, treatment with PPIs was associated with a reduced occurrence of pancreatic pseudocysts [107]. The ESPEN guideline recommended addition of PPI inhibitors for treating patients with an incomplete response to pancreatic enzyme replacement therapy [44]. However, some case reports have highlighted PPI-induced AP [108,109] and hence, the use of PPIs for treatment of AP may need to be reevaluated.

5. Discussion and conclusion

AP is a complex condition characterized by varying severity, ranging from self-limiting, mild disease to more severe cases, subsequently leading to systemic inflammatory response and organ failure [110]. Mortality in SAP patients is estimated to be 25% [5]. With the increasing incidence and burden of AP globally [8], there is a need to identify targeted treatment options and explore novel therapeutic approaches. The existing therapies like fluid resuscitation, analgesics, appropriate nutrition, and antibiotics used to manage the condition are supportive in nature and do not target the etiology of the inflammation. One of the major challenges that remains to be addressed for effective management of AP is to determine timing and frequency of potential pharmacological intervention. Despite advances in the understanding of the pathobiology of AP, there are currently no specific pharmacologic therapies with demonstrated efficacy. Although experimental studies have highlighted the role of antioxidants (including apigenin, glycyrrhizinic acid, and vitamin C) in reducing disease severity, clinical evidence supporting the therapeutic use of these antioxidants is limited. However, recent ESPEN guidelines do recommend glutamine for parenteral nutrition in AP [44]. Among the anticoagulants, LMWH treatment is well tolerated and provides the better prognosis in moderate and severe AP. However, it needs further evaluation in the very early course of AP. Currently there is no evidence from clinical trials that protease inhibitors could alter the course of AP. Other treatment options such as octreotide, lexipafant, and pentoxyfylline have not yielded any promising clinical results. Emerging potential inhibitors including dabigatran, infliximab, spautin-A41, and CM4620-IE as well as novel therapeutic strategies using stem cells and nanomedicine appear to be encouraging but may require additional evidence-based assessments.

Dabigatran, an anticoagulant used for treating patients with atrial fibrillation is an active inhibitor of trypsin which is a key enzyme in AP [65] and is currently undergoing clinical investigation along with standard of care treatment [66]. Infliximab, another promising candidate is a monoclonal antibody against TNF-α and widely used for treatment of inflammatory diseases [85]. TNF-α is a mediator of inflammatory response and plays a key role in pathogenesis of AP [17]. Since TNF-α levels increase early during the disease [38], early administration of anti-TNF treatment by the RAPID-I trial may prove to be an effective strategy for AP therapy. Autophagy inhibitors including spautin-A41 have demonstrated promising activity in experimental studies [100] and await clinical assessment. Additionally, CM4620-IE is a potential calcium channel inhibitor with demonstrated clinical benefits in patients with AP [95], and is currently undergoing further clinical investigation [97]. At present, with a better understanding of immunoregulatory mechanisms, novel immunomodulatory therapies including stem cells are being evaluated and certainly provide new hope for the treatment of SAP. The emerging treatment options of bioactive drugs and novel drug delivery systems for AP treatment in animal studies are also encouraging. Further research on pharmacological agents or intervention strategies that inhibit inflammatory response at the early stage of disease course is warranted to avert subsequent organ failure and mortality risks. Of note, cases of drug-induced AP reported with increasing use of certain drug classes including corticosteroids and proton-pump inhibitors must be considered while selecting treatment options for AP. Interestingly, while the interventional trials for exploring therapy management in AP are mostly performed in adults, studies focussed on pediatric population are limited.

The major challenges affecting the development of targeted therapy for AP include the complex and dynamic process of the disease involving multiple signaling pathways, immune cells, and inflammatory mediators; deficient preclinical research strategies; and inadequate clinical trial designs. Over the past decade, experimental studies have identified several potential pharmacologic therapies, but majority of these failed to exhibit any clinical benefit in patients. Therefore, an ideal therapeutic approach with potential efficacy should be further tested in large, randomized trials with appropriate endpoints for confirmation on optimal activity in clinical practice. In addition, further research efforts are required to elucidate molecular aspects of pathogenesis that trigger systemic inflammatory response followed by multiorgan dysfunction in some patients. Although experimental evidence implicated trypsin as an initiator of AP, definitive proof that protease inhibitors can alter the course of AP is yet to be substantiated with data from clinical trials, currently precluding their inclusion in standard-of-care. In light of recent evidence, immunomodulatory agents that aim to suppress the progression of inflammatory responses could lead to a promising area of therapeutics. Nevertheless, given the multiple operative pathways in AP, it is not clear if future efforts should focus on single-agent therapy or combinatorial strategies targeting several pathways to improve patient outcomes. The success of promising therapy relies on addressing these clinical questions and identifying the key determinants that drive severe outcomes in AP.

The development failures in preclinical research over the past years and current inadequate treatment options for AP underscores the need for reliable and specific biomarkers to better guide therapeutic interventions in a targeted approach. Novel biomarkers or specific inflammatory markers that are expressed during the early stage of AP may facilitate early prediction of the disease. Additionally, biomarkers specific to pathways influencing severity may help in future clinical trial risk stratification and define clear outcomes. Biomarkers may also help to determine differential host response, comorbidities, and risk factors for guiding appropriate 'personalized'

pharmacological approaches for AP. Studies for novel biomarkers by utilizing metabolomics and proteomics platform must be encouraged to pave way for implementing rational therapies.

Adopting a multidisciplinary approach may aid in the optimal management of AP. Lack of specificity, frequency, and timing of pharmacological intervention are key issues with AP which need further clinical evaluation. Additionally, single treatment approach may not be applicable for patients with varying severity in a complex disease such as AP. Early identification of disease symptoms is critical for therapeutic intervention to avoid the inflammatory response and further complications including recurrent pancreatitis. Therefore, clinical studies enrolling patients early (within 24–48 hours of onset of symptoms) may be able to better elucidate high-risk patients and the effect of treatment strategies.

In summary, the potential therapies identified for AP await further development and clinical assessment from large trials to confirm their use in clinical practice. The successful management of AP relies on early diagnosis, risk stratification, and effective treatment interventions which are necessary to alter the course of the disease and must be the focus for future research efforts. Therapeutic targets driving disease severity and outcomes are instrumental for shaping effective treatments for AP and need to be elucidated and evaluated by standardized clinical trials with well-defined endpoints in patient population in the future.

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