Title
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Journal
Pancreas, 47(10)

ISSN
0885-3177

Authors
Abu-El-Haija, Maisam
Gukovskaya, Anna S
Andersen, Dana K
et al.

Publication Date
2018-11-01

DOI
10.1097/mpa.0000000000001175

Peer reviewed

HHS Public Access

Author manuscript

Pancreas. Author manuscript; available in PMC 2019 August 13.

Published in final edited form as:

Pancreas. 2018 ; 47(10): 1185–1192. doi:10.1097/MPA.0000000000001175.

Accelerating the Drug Delivery Pipeline for Acute and Chronic Pancreatitis:

Summary of the Working Group on Drug Development and Trials in Acute Pancreatitis at the National Institute of Diabetes and Digestive and Kidney Diseases Workshop

Maisam Abu-El-Haija, MD[*,†], **Anna S. Gukovskaya, PhD**[‡,§], **Dana K. Andersen, MD**[‖], **Timothy B. Gardner, MD, MS**[¶], **Peter Hegyi, MD, PhD, DSc**[#,**], **Stephen J. Pandol, MD**[††], **Georgios I. Papachristou, MD, PhD**[‡‡,§§], **Ashok K. Saluja, PhD**[‖‖], **Vikesh K. Singh, MD, MSc**[¶¶], **Aliye Uc, MD**[##], **Bechien U. Wu, MD, MPH**[***]

[*]Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center

[†]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH

[‡]Department of Medicine, University of California, Los Angeles

[§]Pancreatic Research Group, UCLA/VA Greater Los Angeles Healthcare System, Los Angeles, CA

[‖]Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

[¶]Department of Medicine, Dartmouth-Hitchcock Medical Center, Geisel School of Medicine, Darmouth University, Hanover, NH

[#]MTA-SZTE Translational Gastroenterology Research Group, University of Szeged, Szeged

[**]Institute for Translational Medicine and First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary

[††]Division of Digestive and Liver Diseases, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA

[‡‡]Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Pittsburgh Medical Center

[§§]Division of Gastroenterology and Hepatology, Veterans Affairs Pittsburgh Health System, Pittsburgh, PA

[‖‖]Department of Surgery, Miller School of Medicine, University of Miami, Miami, FL

[¶¶]Division of Gastroenterology, Department of Medicine, University of John's Hopkins, Baltimore, MD

Address correspondence to: Maisam Abu-El-Haija, MD, Pancreas Care Center, Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave MLC 2010, Cincinnati, OH 45229 (Maisam.Haija@cchmc.org).

Supplemental digital contents are available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pancreasjournal.com).

[##]Stead Family Department of Pediatrics, University of Iowa, Stead Family Children's Hospital, Iowa City, IA

[***]Center for Pancreatic Care, Department of Gastroenterology, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA.

Abstract

A workshop was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases to focus on research gaps and opportunities on drug development for pancreatitis. This conference was held on July 25, 2018, and structured into 3 working groups (WG): acute pancreatitis (AP) WG, recurrent AP WG, and chronic pancreatitis WG. This article reports the outcome of the work accomplished by the AP WG to provide the natural history, epidemiology, and current management of AP; inform about the role of preclinical models in therapy selection; and discuss clinical trial designs with clinical and patient-reported outcomes to test new therapies.

Keywords

acute pancreatitis; drug therapy; trials; molecular targets

Acute pancreatitis (AP) is defined by meeting 2 of the following 3 criteria: abdominal pain and symptoms suggestive of pancreatitis, lipase and/or amylase 3 times the upper limit of normal, and image findings of AP.[1,2] Acute pancreatitis is a leading cause of emergency department visits and gastrointestinal (GI) admissions in the United States.[3–5] Hospitalizations costs are well more than $2 billion annually.[6] This constitutes a health and economic burden with increased hospitalizations, medications, lost work, and school time for the patients and caregivers. There has been increasing trends in incidence of AP in adults with 30 to 100/100,000 (250,000 cases per year in the United States alone[7,8] and in children up to 13/100,000 per year).[9–13] In most patients, pancreatic damage ultimately resolves, but in severe cases, unremitting persistent systemic inflammatory response (SIRS) leads to multiple organ (especially lung) failure, a major cause of mortality among patients with AP. In adult cases, AP has a mortality rate of up to 6%,[14] but as many as 50% of patients with severe disease associated with persistent multiorgan dysfunction have a risk of death.[14–16] Most cases in children are mild, with a subset that progress to severe AP (SAP) with increased risk of complications, prolonged length of stay (LOS), and significant morbidity.[17–19] Severe AP in children represents 15% to 30% of all cases depending on the definition used.[19–22] With the rise in AP incidence and its high morbidity rates,[17–19] significant advances in prevention and treatment are urgent. However, we strongly believe that the incidence rate is still much higher than currently diagnosed. A multinational prospective clinical trial aiming to answer the real incidence rate of AP in children is in process (Pain in Early Phase of Pediatric Pancreatitis [PINEAPPLE] trial).[23]

Pancreatitis has been associated with gallstones, alcohol abuse, hypertriglyceridemia, and genetic factors. Hallmark responses of AP include hyperamylasemia, inappropriate activation of digestive enzymes (eg, conversion of trypsinogen to trypsin), accumulation of large vacuoles in acinar cells, induction of pro-inflammatory signals (eg, the key

transcription factor nuclear factor-κB [NF-κB]) resulting in inflammatory cell infiltration in the pancreas, an SIRS and acinar cell death through apoptosis and necrosis.[24,25] The pathogenesis of AP is not fully understood, but evidence from basic science studies indicates critical roles for pathologic calcium signals, NF-κB, and zymogen activation.[26] Other observations in experimental and human AP have shown the formation of cytoplasmic vacuoles in acinar cells that represent disordered autophagy. Activation of trypsinogen to trypsin occurs then possibly through cathepsin B in these abnormal autophagic vacuoles.[27] Furthermore, the mechanisms leading to trypsinogen activation as well as how trypsin causes AP are largely unknown. Recent insights into the pathogenic mechanism of pancreatitis provided novel information on role of acinar cell organelle disorders in AP.[25,28]

Despite advances in understanding of the pathobiology of AP,[25] there is currently no pharmacologic therapy that has demonstrated efficacy in altering the natural history of the disease course. As a result, the mainstay of treatment continues to be entirely based on supportive care and management of complications.

A barrier to drug development in AP is the reduction in investment on novel drug research and development (R&D) that is part of a larger overall trend. Research investment in novel drug R&D decreased from US $21 billion (2004–2008) to $17 billion (2009–2013). Unfortunately, the biggest decrease was in GI diseases (62% from US $828 million to $311 million). Furthermore, the relative research activity in pancreatitis dropped from 25.7% to 10.7% in the last 50 years compared with other GI inflammatory disorders.[29]

The objectives of the AP working groups were to address the following 4 main domains pertinent to development of drug therapy in AP: (1) natural history, epidemiology, and current management; (2) preclinical models and animal models of AP; (3) potential therapeutic targets; and (4) risk stratification and patient selection.

NATURAL HISTORY AND CURRENT MANAGEMENT OF AP

According to the revised Atlanta classification, approximately 2/3 of AP is categorized as mild, 20% to 30% moderate, and 5% to 10% as severe. The overall mortality is up to 6%.[14] As many as 50% of patients with severe disease have a risk of mortality.[14–16] In children, most patients experience mild disease, with 15% to 34% developing SAP with attendant morbidity and mortality.[19–21] A paucity of prospective studies is an obstacle to understanding the natural history and identification of risk-stratified therapies in pediatric AP

Biliary and alcoholic pancreatitis are the 2 most common causes of AP in adults,[30,31] whereas pediatric cases are associated with a variety of etiologies that encompass biliary, metabolic/systemic factors, hereditary, and anatomic anomalies.[12,32–34]

In terms of risk factors in adult SAP, there have been several risk factors studied including aging, comorbidities, hypertriglyceridemia, elevated body mass index, and pre-existing diabetes.[35] A number of scoring systems and simple laboratory markers have been developed with the aim of predicting prognosis during the early phase of AP. Hemoconcentration, elevated blood urea nitrogen, elevated C-reactive protein, an elevated

Ranson score, APACHE (Acute Physiology And Chronic Health Evaluation) II score, and SIRS have been associated with severe AP. However, the accuracy of both individual or combination of scoring systems, such as BISAP (Bedside Index of Severity in Acute Pancreatitis), or the HAPS (Harmless Acute Pancreatitis Score), needs to be improved.[36–38] To date, there is no validated pediatric severity scoring system.[39,40] The applicability of various clinical scoring systems for intervention trials in AP is described hereinafter in the discussion on risk stratification.

In respect to current management, early (first 24 hours) adequate intravenous fluid resuscitation, enteral feeding in predicted severe AP, early endoscopic retrograde cholangiopancreatography in biliary AP with concomitant biliary obstruction or cholangitis, and delaying surgical interventions for infectious complications have been shown to be of high importance. The most common local complication is peripancreatic fluid collections, whereas the most common distant organ failure is lung injury. Importantly, centralized care improves, whereas deviation from the recommendations of the International Association of Pancreatology/American Pancreatic Association evidence-based guidelines was found to worsen, the outcome of AP[41]

PRECLINICAL/ANIMAL MODELS IN AP RESEARCH

The pathophysiologic mechanisms of AP are not completely known.[26,42] Mechanistic studies have been largely performed in rodent tissues because human tissue is difficult to obtain during the disease process. Recent studies in pancreatic parenchymal cells have revealed that pathobiologic pathways in rodent and human tissue are probably the same. In the context of drug development, it is important to determine the suitability of various experimental animal models for testing of potential novel therapeutic agents.

For the past several decades, different species have been used in experimental studies,[43–49] but currently, mice are preferred because of the availability of strains with specific genetic deletions, low-cost housing, and other resources related to this species.[50–53] In the animal models, the disease is induced experimentally by common duct ligation, hyperstimulation using cholecystokinin analogs, retrograde injection of bile acids, or other chemicals or dietary modifications.[54] The end result of such insults is acute pancreatic inflammation and necrosis of varying severity with symptoms resembling clinical disease. These models have been used extensively by investigators to understand the mechanism of the disease as well as preclinical models for testing of therapeutic agents. Methods of induction of disease may or may not have an etiological equivalent for human disease, and this limitation has often been used to criticize the relevance of a model to the human disease.[55] Using these experimental animal models, the “auto digestion hypothesis” and role of “gall stone-induced blockage of pancreatic flow or influx of bile in pancreatic duct” in biliary pancreatitis have been rigorously tested and published.[56–59] Based on these studies, consensus exists regarding the early activation of digestive enzymes in the pancreas in response to insult and pancreatic acinar cells being the primary site of initiation of injury in AP[60] Whether the blockage of pancreatic flow itself is sufficient in inducing AP or the influx of bile is required to trigger the disease was answered by the development of an animal model with anatomical similarity to the human pancreatic biliary ductal system.[59,61]

Although these animal-based experimental models have helped us understand the steps involved in the initiation and progression of the disease, there are several limitations. Human patients comprise a diverse population with different genetic backgrounds and different epigenetics and dietary preferences, which, on their own or in combination, can contribute to susceptibility, severity, and progression of the disease. In animal models, full recovery is mostly observed although in patients, the disease might follow a complicated course with extended hospitalization. The distribution of bile acid surface receptors is different in rodent acinar and human cells, thereby making the applicability of the conclusions from rodent models to human disease difficult. Overall, experimental animal models are important for understanding the disease mechanism but due considerations should be given to the dissimilarities in rodent and human pancreatitis when extrapolating these findings in animals for developing strategies to treat human AP

POTENTIAL MOLECULAR TARGETS IN AP

The current paradigm is that AP originates in injured acinar cells. Its manifestations (responses) are inappropriate, intra-acinar activation of digestive enzymes, in particular conversion of trypsinogen into active trypsin, dysregulation and inhibition of secretion, and activation of inflammatory transcription factors, followed by the inflammatory cell infiltration and necrosis, which are the major determinants of disease severity.[4,24,25] Experimental studies strongly indicate that the inflammatory, especially neutrophilic, response in AP is nonresolving/un(der)controlled, and its down-regulation could have beneficial effects. To date, our knowledge of the inflammatory response in pancreatitis has not translated into effective therapies. One cause of nonresolving inflammation in AP could be unremitting acinar cell injury, which perpetuates the inflammatory response—a vicious cycle of parenchymal necrosis and immune cell infiltration.

Considerable progress has been achieved during the last decade in elucidating the nature of acinar cell injury leading to AP. Several critical cellular processes that become disordered in acinar cells have been elucidated and shown to drive (or even initiate) AP. In particular, pancreatitis causes disordering of autophagy, the principal catabolic cellular pathway for degradation, and recycling of unneeded or dysfunctional cytoplasmic organelles.[28,62,63] This results in accumulation in acinar cells of large vacuoles with poorly degraded cargo, a long-noted feature of pancreatitis. Impaired autophagy is a common feature of all experimental AP models and is prominent in human disease.[28,62,63] Recent studies in genetic models[64–67] provide mechanistic insights into the role of autophagy in pancreas: autophagy blockade or impairment triggers spontaneous pancreatitis in 4 different knockout mouse strains. These findings indicate that enhancing autophagic efficiency could be a promising approach for AP treatment. Impaired/inefficient autophagy is a common feature of various neurodegenerative diseases, and pharmacologic agents are being developed to normalize autophagy in these diseases. These approaches should be tested for AP in preclinical studies. For example, it was found that the disaccharide trehalose, known to enhance autophagy and improve the outcome in neurodegenerative diseases, greatly ameliorates pathologic responses in 2 mouse models of AP.[68]

Mitochondrial dysfunction is another key organelle disorder both in acinar and ductal cells found in AP.[28,68–74] Pancreatitis causes persistent opening of a nonselective channel in the mitochondrial membrane, called the permeability transition pore, resulting in mitochondrial depolarization and fragmentation followed by drop in ATP level—features prominent in various experimental AP models and in human disease. The protein cyclophilin D is a key mediator of mitochondrial membrane permeability transition pore opening, and studies have shown that genetic or pharmacologic knockdown of cyclophilin D abolishes or greatly reduces both local (pancreatic) and systemic pathologic responses in multiple experimental models of AP[28,68–70] These findings validate restoring mitochondrial function as a promising approach for AP treatment.[68] In this regard, a UK-based company is pursuing preclinical development of cyclophilin D inhibitors for potential treatment for AP. In addition, a registered multicenter randomized double-blind clinical trial investigating the effects of high energy in the early phase of AP (high- vs low-energy administration in early phase of pancreatitis [GOULASH] trial) is currently ongoing.[75]

The physiologic digestive enzyme secretion from acinar cells is mediated by oscillatory increases of cytosolic Ca^{2+} triggered in response to neurotransmitters such as acetylcholine. The increases result from Ca^{2+} released from endoplasmic reticulum (ER) stores and are transient because the released Ca^{2+} is rapidly reuptaken into the stores. In contrast, several AP triggers, such as bile salts, or acinar cells' hyperstimulation with cerulein, cause massive and persistent Ca^{2+} release from ER stores resulting in their sustained Ca^{2+} depletion.[76,77] In this state, the acinar cell attempts to refill ER stores by Ca^{2+} entry through the activation of the plasma membrane CRAC channel,[76,77] resulting in sustained increase in cytosolic Ca^{2+}. Sustained increase in cytosolic Ca^{2+} causes acinar cell damage through several pathways directly or through activating the Ca^{2+}-dependent phosphatase calcineurin. For example, increase in cytosolic Ca^{2+} causes its uptake by mitochondria leading to mitochondrial Ca^{2+} overload, which in turn causes mitochondrial depolarization, decrease in ATP synthesis and, ultimately, necrosis.[69,70] Calcineurin further exacerbates mitochondrial dysfunction by promoting mitochondrial fragmentation.[78] In addition, Ca^{2+} directly and through calcineurin stimulates activation of the pro-inflammatory transcription factors NF-κB and NF-AT.[79] Recent reports demonstrate that approaches to inhibit the CRAC channel or prevent calcineurin activation both attenuate experimental pancreatitis, suggesting them as important targets for disease treatment.[76–81] The importance of calcium toxicity has also been widely investigated in pancreatic ductal cells. Bile acids, fatty acids, ethanol, and even the activated trypsin have been shown to trigger 2 phases toxic calcium elevation causing decreased fluid and bicarbonate secretion.[82–84] Of note, one of a series of CRAC inhibitors (developed by a US-based company) has reached a phase I clinical trial.[85]

Finally, pancreatic fluid and bicarbonate secretion seems to be protective against AP. Pancreatitis induced either aquaporin $1^{-/-}$, $CFTR^{-/-}$, or $NHERF1^{-/-}$ mice resulted more severe pancreatitis.[86–88] On the other hand, all pancreatitis inducing factors were shown not only damaging to the acinar cells but also decreasing fluid and bicarbonate secretion as well.[58,88,89]

Table 1 lists potential approaches for AP treatment, including normalizing autophagic, mitochondrial functions, blocking Ca^{2+} influx through CRAC channels, and inhibiting Ca^{2+}-dependent phosphatase calcineurin.

RISK STRATIFICATION AND SUBJECT SELECTION

A patient is given a diagnosis of AP by meeting 2 of the following 3 criteria: upper abdominal pain and symptoms suggestive of pancreatitis, serum lipase and/or amylase 3 times the upper limit of normal, and image findings of AP on cross-sectional imaging.[1,2]

Identification of Complication Risk

Both local (pancreatic or peripancreatic) complications as well as systemic complications (distant organ failure) may occur in the setting of AP. Consensus-based definitions for complications related to AP have been previously described and incorporated into classification systems for categorizing the severity of AP.[1,90] The most widely recognized complications of AP are pancreatic necrosis and distant organ failure (respiratory failure, renal failure, and/or circulatory shock). Both the revised Atlanta criteria and determinants-based classification systems make a distinction according to the duration of organ failure with emphasis placed on persistent (>48 hours) organ failure as the most ominous complication defining SAP.

Although the frequency of major complications related to AP is relatively low, the consequences of SAP can be life-threatening. As such, substantial effort has been devoted to developing strategies for early identification of patients at increased risk for complications related to AP. Numerous approaches to risk stratification have been developed that include clinical prediction scores, biochemical parameters, and machine learning algorithms.[36] A comparison of 9 scoring systems in 2 prospectively collected cohorts of patients hospitalized for AP did not demonstrate clear advantage in terms of accuracy for any specific approach to identify patients at increased risk for persistent organ failure.[36] As a result, most clinical practice guidelines[41] currently recommend the use of a simplified assessment system such as the SIRS syndrome score that comprises vital signs and laboratory parameters to assess the extent of systemic inflammation related to an AP episode. It should be noted that SIRS is not specific to AP. However, previous studies have demonstrated an association between the duration of SIRS (lasting>48 hours) with persistent organ failure as well as mortality in AP.[1,41]

Definition of Endpoints/Outcomes

Selection of study end points in AP should be determined based on the context of the proposed intervention. Traditional approaches for development of novel therapeutics in AP have focused on prevention of severe forms of illness. These studies incorporated initial risk stratification to identify a higher-risk subgroup of patients for outcomes such as persistent organ failure or mortality.[91] In these trials, organ failure is typically defined based on an established scoring system such as the Modified Marshall Score (Atlanta) and mortality is typically defined as in-hospital death.[1]

Additional outcomes to be considered in AP might include amelioration of disease or expedited recovery. Length of stay has often been reported in studies of AP.[92,93] However, LOS is problematic as an outcome parameter because it can be influenced by factors unrelated to the disease process and is a poor overall measure of disease activity. To address these limitations, a disease-specific activity measurement scale has recently been developed through a consensus-based process.[94] This scale, the Pancreatitis Activity Scoring System (PASS), comprises the following 5 domains: ability to tolerate oral intake, abdominal pain, opioid requirement, SIRS, and organ failure. Each of these components is given a weighted score with the total score represented as the sum of each individual category. The score is designed to be calculated based on 12-hour intervals to reflect dynamic changes in disease status. In a validation study using a prospective cohort of consecutively admitted patients (excluding hospital transfers), an elevated PASS at admission (>140) was shown to be associated with increased risk of moderate and severe pancreatitis whereas a discharge PASS of greater than 60 was associated with increased risk of early rehospitalization.[95]

Critical Path Innovation Meeting

To explore the next steps in development of clinical outcome assessment (COA) tools in AP, a Critical Path Innovation Meeting was convened with members from the Food Drug Administration (FDA) Center for Drug Evaluation and Research on October 26, 2017. The intent of the meeting was to learn more about the FDA drug development tool qualification process as well as discussion regarding additional considerations for further development of the PASS instrument as a COA in AP. The findings from the meeting are intended to be available in the public domain and a summary of the meeting is included as Supplemental Digital Content 1, http://links.lww.com/MPA/A683.

Performance Characteristics of Measures

In a previous systematic literature review of clinical trials in AP involving human subjects, 61 studies were identified from 1996 to 20 1 4.[96] The most common primary outcome was mortality (16%). Other common outcome parameters included organ failure (15%), pancreatic infections (13%), and SIRS (10%). Included in the review were 9 studies that evaluated pharmacologic intervention in AP.[96]

Among these trials, the Lexipifant study merits special consideration because the study design reflects most closely the established paradigm for testing early intervention in AP. In this phase III study, investigators in the United Kingdom conducted a large scale multicenter trial to evaluate the impact of early treatment (initiation of therapy within 72 hours of symptom onset) on disease course in patients with predicted severe AP[91] The primary outcome measure was incidence of complications (organ failure, necrotizing pancreatitis, or acute fluid collections). The study was powered based on an assumed reduction from a 40% complication rate in the placebo arm to 24% in the intervention arm. However, after completing the trial, the investigators noted that only 14% of enrolled study participants developed new-onset organ failure. In addition, assessment of local complications (necrosis, fluid complications) was complicated by the fact that cross-sectional imaging was performed in less than half of the study participants (45% in placebo group, 38% in the intervention arm).

As a case study, the Lexipifant trial highlights several of the challenges with studying the impact of widely accepted outcome parameters such as persistent organ failure or necrosis. In the case of the former, organ failure is a rare outcome even among patients with predicted severe disease. In the case of necrosis, this is a radiographic finding that can be problematic with respect to ascertainment given not all subjects will typically undergo cross-sectional imaging during hospitalization.

Subject Selection for Drug Trials and Time of Treatment

A major challenge in designing clinical trials for testing new drug treatments in AP relates to participant selection as well as timing of intervention. Work from previous observational studies has shown that the precision with which a patient's outcome can be predicted increases over time. However, delays in initiating therapy may limit the subsequent observable effect of an intervention. The following potential strategies address the following limitations:

-Recruitment of all potentially eligible participants with established AP irrespective of disease severity.—This trial design would be best suited for low-cost interventions intended to ameliorate the overall disease course. Advantages of this approach would include rapid accrual and the ability to initiate intervention as early as possible as well as the ability to broadly generalize the study findings to the AP population at large. Disadvantages of this approach would include limited feasibility to assess for outcomes such as persistent organ failure or necrosis given the anticipated low incidence in the general AP population.

-Stratified randomization based on initial markers of disease severity.—Ensuring equal distribution of participants at risk for severe illness is paramount in circumstances where the impact of an intervention may vary based on the extent of disease activity (effect modification). In these settings, stratified randomization based on markers of initial disease severity available at the time of enrollment will help ensure balanced representation across the study arms. An adaptive study design with a priori criteria to evaluate for feasibility can help target further enrollment criteria after planned interim analysis.

-Randomization after "run-in" period.—Newly developed drugs that can prevent or diminish complications related to SAP are of critical importance. However, such agents will likely bear increased cost related to the expense associated with drug development. As a result, these newer agents will most likely be used as second-line therapy in clinical practice reserved for those patients not responding to standard resuscitation protocols. A trial design that incorporates a run-in period can be used to reflect this reality as well as enrich the study population with patients most likely to experience severe forms of AP. In this study design, eligible patients are identified at the time of presentation to the hospital but randomization only occurs once they have undergone a period of initial fluid resuscitation to evaluate for ongoing eligibility.

Logistical and Regulatory Issues in AP-Related Drug Trials

A number of logistical and regulatory factors must be addressed to successfully conduct early intervention trials in AP. One challenge is that patients may present at various times in their disease course, which would make the initiation of therapy at an “early”-stage difficult. The effect of timing with respect to onset of symptoms and initiation of therapy is an important consideration. Future trials should either incorporate the timing of symptom onset in their eligibility assessment criteria or at least carefully record this information for study participants to ascertain the optimal therapeutic window for future treatment.

Similar to other serious acute illnesses, caring for patients hospitalized for AP involves coordination among multiple disciplines including emergency medical teams, inpatient care services, as well as potentially intensive care units or surgical teams. As a result, a successful trial requires the participation of multiple investigative teams comprising all providers that may be involved in the care of patients with AP.

Several key steps are needed to facilitate regulatory approval of new agents for treatment of AP. First is the development of disease-specific clinical end points to demonstrate efficacy of a new therapeutic intervention. An overview of the development of COA as part of a drug development tool qualification program can be found at the FDA website (https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram_.

Types of COAs include patient-, clinician-, or observer-reported outcomes as well as performance outcome measures. Of particular interest are patient-reported outcomes (PROs), which have not been thoroughly evaluated in AP. In addition, long-term outcomes of AP merit further consideration. With the recent observations that 15–30% of patients develop impaired glucose tolerance or diabetes within 3 years after a single episode of AP,[97,98] it is important to follow patients for longer observation periods after treatment. Furthermore, recent studies have shown that the quality of life of patients remains impaired in the long term after an AP attack.[99]

RESEARCH GAPS AND OPPORTUNITIES

As the study of AP has evolved from natural history and epidemiology, to pathophysiology defined through preclinical models, to potential targets and clinical trial design, a number of factors remain, which are required to improve outcomes through the design of the next phase of human intervention studies.

- In terms of patient selection and defined outcomes, methods of defining pathobiologic pathways and severity are needed. This will allow a more “personalized” approach to therapy.
- Early prediction of SAP through novel blood and imaging biomarkers are needed.
- Patient-reported outcomes in AP are not well studied nor are PROs defined to measure the impact of AP on patients’ lives.

- Patient-reported outcomes on pain, nutrition and quality of life should be developed for trials.
- The most important end points of clinical trials are death and end-organ failure, but surrogate outcomes of severity such as C-reactive protein and procalcitonin need to be validated.
- The time points for follow up ranging from inpatient admission, to recovery, to post discharge are not well defined. Long-term follow up is lacking in most studies.
- Effect of disease beyond AP such recurrent AP, chronic pancreatitis, exocrine and endocrine insufficiency are poorly studied. These outcomes should be considered in study designs.
- Although most studies have focused on patients with predicted severe outcomes, including all AP patients at onset of disease may be the most appropriate approach to observe the prevention of progression to SAP, given the limitations of the prognostic scoring systems for predicting severity.

CONCLUSIONS

The workshop examined all aspects of AP from basic patho-physiology in preclinical models, and potential targets to clinical presentation, diagnosis, current management, severity predictive models to the defined outcomes. Studies that included adults as well as childhood AP were reviewed. Several gaps in the current understanding and management of AP were identified. Without addressing these gaps in designing clinical trials for treatment of AP, no further progress can be made. AP is the leading GI disease for emergency department visits and hospitalizations, and therefore warrants further studies dedicated to target negative outcomes. The lack of animal models that mimic human disease remains a hindering factor to progress. Biomarkers to detect severity and disease pathways early on presentation are desperately needed to stratify patients with AP and allow targeted therapy designs. Future study designs should require input from regulatory agencies, focus on patient-related outcomes, develop well-defined and objective clinical outcomes to ensure progress in the management of AP that involves all stakeholders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors thank the National Pancreas Foundation for the support, the members of the Food Drug Administration for consultation, and Ms. Joy Merusi of the University of Pittsburgh and Ms. Rachel Pisarski of The Scientific Consulting Group, Inc, for logistical support.

The Hungarian National Research, Development and Innovation Office (K116634, KH125678). M.A.H, A.S.G., S.J.P., A.K.S., A.U., and B.U.W acknowledge support from U01–108300 and others, which represent the Consortium for the Study of Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC). M.A.H. is supported by NIDDK (Grant Number 1K23DK118190–01). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

VS. is a consultant to Abbvie, Akcea Therapeutics, and Ariel Precision Medicine; A.U. is a member of American Board of Pediatrics, Subboard of Pediatric Gastroenterology; G.P. received grant support from Abbvie and is a consultant to GlaxoSmithKline and Abbvie.

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TABLE 1.

Potential Molecular Targets for AP Therapy

Cellular Process to Target	Association With AP		Genetic Approaches	Pharmacologic Approaches
	Experimental	Human		
Impaired autophagy	Shown in 10 experimental and genetic pancreatitis models	Associated with human disease	Genetic approaches to block autophagy trigger spontaneous pancreatitis in 4 genetic mouse models	Enhancing autophagy efficiency with trehalose prevented or alleviated pathologic responses in 2 mouse models in AP
Mitochondrial dysfunction	Shown in 9 experimental and genetic pancreatitis models	Associated with human disease	Genetic approaches to restore mitochondrial function ameliorate AP in all models tested	Pharmacologic approaches to restore mitochondrial function greatly ameliorated AP severity in 4 models tested
Excessive Ca^{2+} influx	Shown in at least in 3 experimental pancreatitis models	?	?	Pharmacologic approaches to block CRAC channel alleviate AP in 3 models tested
Calcineurin activation	Shown in a mouse model of post-ERCP pancreatitis	?	Genetic approaches to block calcineurin alleviate inflammation	Pharmacologic approaches to inhibit calcineurin alleviate inflammation in a mouse model
CFTR	Shown in at least in 3 pancreatitis models	Associated with human disease	Deletion of CFTR in at least 3 animal models trigger spontaneous pancreatitis	VX-770 and VX-809 restore the expression cystic fibrosis transmembrane conductance regulator of CFTR

ERCP indicates endoscopic retrograde cholangiopancreatography.