Pancreatology 12 (2012) 119–123

Contents lists available at SciVerse ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

Recombinant human activated protein C as a disease modifier in severe acute pancreatitis: Systematic review of current evidence

Charles J. Miranda, Benoy I. Babu, Ajith K. Siriwardena*

Hepatobiliary Surgery Unit, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK

Keywords:
Human recombinant activated protein C
Drotecogin Alfa
Pancreatitis

A B S T R A C T

Background: The severity of organ failure caused by acute pancreatitis (AP) is the most important determinant of mortality in the disease. Recombinant human activated protein C (Drotrecogin Alfa; Xigris, APC, rhAPC) is the first drug to show a decrease in all-cause mortality due to multiple organ failure caused by sepsis. As the systemic inflammatory response syndrome (SIRS) that causes organ failure in early AP is similar to that caused by severe sepsis, the use of rhAPC in the management of AP has been investigated in experimental and clinical studies which are collated in this review.
Methods: A literature review of published material identified from MEDLINE and EMBASE databases, for the period from January 1985 to January 2011, reporting rhAPC usage in AP.
Results: 3 of 4 experimental studies reported an improvement in outcome in animals with AP given rhAPC. The clinical randomized trial showed no improvement in outcome in the treatment arm.
Conclusion: The experimental evidence of disease amelioration in AP following intervention with rhAPC has not translated to the small clinical RCT. Given that there were only 16 patients in the treatment arm, further clinical evaluation is justified.

1. Introduction

Severe acute pancreatitis (SAP) is characterized by the co-existence of local peri-pancreatic complications with sustained organ failure [1]. The treatment remains essentially supportive and comprises careful and adequate fluid resuscitation together with support for cardiovascular, respiratory and renal systems in addition to appropriate analgesia [2,3]. Prophylactic antibiotic therapy [4–6], early enteral nutrition [7,8] and early endoscopic sphincterotomy [9] for patients with biliary acute pancreatitis and features of bile duct obstruction are the only specific interventions for which there is supportive randomized trial evidence. However, none of these interventions are universally accepted as genuinely ameliorating the disease course and in the case of antibiotics in particular, current guidance does not favor prophylaxis.

Given that the early stage of severe acute pancreatitis does not require surgical intervention [10,11], this phase of the disease is ideally and logically suited to pharmacological intervention aimed at disease modification. Many drugs have been evaluated as specific pharmacological treatments for severe acute pancreatitis. Disappointingly, the unifying characteristic of the drugs that have been evaluated to date has been their lack of efficacy as effective disease-ameliorating treatments for severe acute pancreatitis. Whilst it is thought that some of this apparent lack of efficacy may relate to the over-broad categorization of severe acute pancreatitis in the 1992 Atlanta consensus criteria [1] resulting in patients with transient or minimal organ failure (and thus a likely mild clinical course) being incorrectly categorized as severe, it remains the case that there is to date, no specific pharmacological treatment for severe acute pancreatitis.

One strategy in the search for specific interventions is to consider treatments that have been effective in disease states that are similar to SAP. Severe sepsis has similarities to SAP; both are characterized by an exaggerated systemic inflammatory response syndrome (SIRS). Inflammation involves a pathophysiological derangement of the endogenous anticoagulant pathways involved in the maintenance of microvascular patency [12] with microvascular thrombosis and disseminated intravascular coagulation being a critical outcome [13]. The protein C pathway plays a major role in preventing microvascular thrombosis [14]. Endogenous protein C is depleted in a primate model of *Escherichia coli*-induced sepsis resulting in microvascular thrombosis, the harmful effects of which are ameliorated by intravenous infusion of recombinant human active protein C molecule (rhAPC) [15]. Based on these key

* Corresponding author. Tel.: +44 161 276 4250; fax: +44 161 276 4530.
E-mail address: ajith.siriwardena@cmft.nhs.uk (A.K. Siriwardena).

1424-3903/$ – see front matter
doi:10.1016/j.pan.2012.01.002

experimental findings, human recombinant activated protein C (Xigris, Eli Lilly, Indianapolis, IN) was evaluated in a major randomized trial in patients with sepsis (the PROWESS study [16]). The PROWESS study demonstrated that treatment was associated with a significant reduction in mortality.

SAP is characterized by pancreatic and peri-pancreatic necrosis in addition to SIRS. Microvascular thrombosis is likely to be one of the mechanisms involved in the mediation of pancreatic necrosis. Thus a hypothetical case can be made that Xigris may have a role as an early and specific disease-modulating drug in SAP for its roles in maintaining microvascular patency and down regulating the inflammatory response.

An important caveat is that acute pancreatitis was one of the listed exclusion criteria in the PROWESS study [Appendix 2 [16]]. SAP is associated with a risk of peri-pancreatic hemorrhage and thus the use of a drug with potent anticoagulant properties may lead to bleeding-related complications.

The potential role of rhAPC as a specific pharmacological treatment for SAP was recognized by Alsfasser and colleagues who undertook the first evaluation of this drug in this setting [17]. Since their initial report, experience with RHAPC in experimental acute pancreatitis has accrued and a small clinical randomized trial has also been undertaken.

Considering the history of unsuccessful pharmacological interventions in SAP the aim of this study is to undertake a detailed systematic review of the evidence for rhAPC as a disease modifier and to address whether there is sufficient evidence for an appropriately constituted randomized trial to evaluate this drug in SAP.

2. Methods

2.1. Literature search and data retrieval strategy

A computerized search was performed of the MEDLINE and EMBASE databases for the period from January 1985 to January 2011 using the OVID search engine (Version 10.5.1, Source ID 1.13281.2.21; Ovid Technologies, Inc., New York, NY, USA). The search terms 'Pancreatitis', 'Protein C', 'Activated Protein C' and 'Drotrecogin' were used. The map term to subject (MeSH) heading was employed where possible. Results were combined with the keywords, with the aid of Boolean operators. There were 23 hits in MEDLINE and 61 in EMBASE. The Cochrane systematic reviews methodology was utilized to cross-reference combined EMBASE and MEDLINE output with all clinical trials and studies including experimental studies and any non-English studies. Letters and reviews without original data were excluded, leaving a final study population of 8 manuscripts. The reasons for excluding manuscripts are provided in Fig. 1.

All retrieved manuscripts were reviewed by two authors (CJM, BIB) and any difference of opinion regarding final inclusion/exclusion was resolved by discussion with the third author (AKS).

3. Results

3.1. Human recombinant activated protein C in experimental acute pancreatitis

Four studies have evaluated the role of rhAPC in experimental acute pancreatitis [17–20] (Tables 1 and 2). Of these, a further study by Chen's group was excluded, as there is a considerable apparent overlap between the 2007 study [19] and the 2010 report [21].

All experimental studies have evaluated experimental acute pancreatitis in the rat model. There are no data on large animal models of acute pancreatitis. All use a well-validated intra-ductal infusion method to induce acute pancreatitis. A wide range of concentrations of human recombinant activated protein C is evaluated.

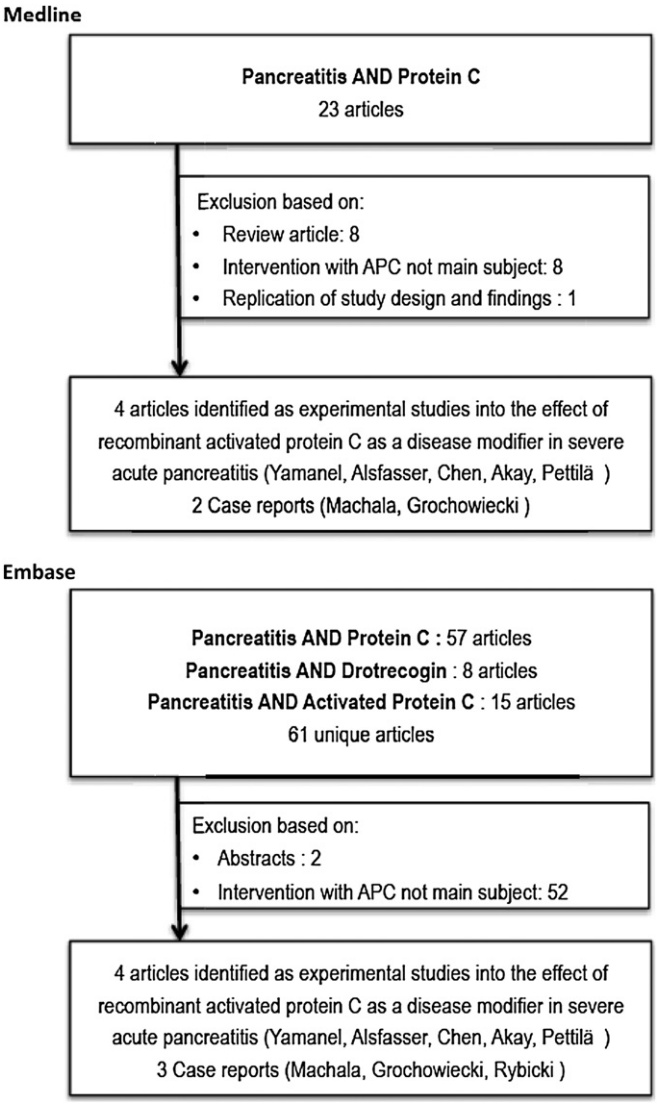

Fig. 1. Search strategy. Date range from January 1985 to January 2011. rhAPC = human recombinant activated protein C. AP = acute pancreatitis.

The findings are not consistent. Yamanel and colleagues [18], using 100 mg/kg rhAPC as a single dose at 6 h after induction, report improvements in histologic features of pancreatic injury, serum markers of inflammation and a reduction in bacterial translocation. There was no evidence of pancreatic or intra-abdominal hemorrhage.

Alsfasser's [17] comprehensive report describes a concentration-dependent thrombocytopenia but no effect of the drug on histologic scores of necrosis and edema with the 100 μg/kg/h continuous infusion. The Alsfasser group is the only study to examine mortality and they show a significant reduction in mortality in animals with AP treated with rhAPC compared to animals with AP alone.

Chen's study [19] provides detailed information on the effect of rhAPC on the mitogen-associated protein kinase pathway demonstrating a reduction in expression of stress proteins.

The Akay study [20] findings are in contrast to the others in that they report no beneficial effects from intervention with rhAPC. Of note, the concentration of rhAPC used in their study parallels the dose used in human sepsis (24 μg/kg/h).

Table 1
Protocol details of studies evaluating human recombinant activated protein C in experimental acute pancreatitis. rhAPC = Human recombinant activated protein C; AP = Acute Pancreatitis; i.v. = Intravenous; MAPK = mitogen-activated protein kinases. CNI1493: a synthetic inhibitor of signal transduction, which inhibits phosphorylation of p38 MAPK.

First author	Animal model	Study designation/ detail	Induction agent/route	Concentration of Xigris	Groups	Number of animals	Study duration
Yamanel [18] 2005	Rat	Effect of rhAPC on AP	Intra-ductal 5% sodium taurocholate	100 mg/kg single dose at 6 h after induction	Group I = control Group II = AP Group III = AP + rhAPC	45	24 h
Alsfasser [17] 2006	Rat	Safety assessment of rhAPC	Intra-ductal saline plus i.v. cerulein 5 μg/kg/h for mild AP Intra-ductal 10 mM glycodeoxycholic acid–glycylglycine and i.v. cerulein (as above)	0.6 mL/kg/h or 100 μg/kg/h Continuous infusion	Dose-ranging study: 12.5, 17, 21, 50 and 100 μg/kg/h rhAPC	15 (3 per group)	6 h
Alsfasser [17] 2006	Rat	Treatment of severe AP	Intra-ductal 10 mM glycodeoxycholic acid–glycylglycine and i.v. cerulein	100 μg/kg/h Continuous infusion	Group 5: severe AP Group 6: severe AP and rhAPC	24 (12 per group)	6 h
Alsfasser [17] 2006	Rat	rhAPC & survival	Intra-ductal 10 mM glycodeoxycholic acid–glycylglycine and i.v. cerulein	100 μg/kg/h Continuous infusion	Group 7: severe AP Group 8: severe AP and rhAPC	16 (2 groups)	24 h
Chen [19] 2007	Rat	Effect of rhAPC on MAPK	Intra-ductal 5% sodium taurocholate	10 μg/kg (low dose) or 50 μg/kg (high dose)	5 groups: Control AP AP + rhAPC low dose (10 μg/kg) AP + rhAPC high dose (50 μg/kg) AP + CNI1493*	75	16 h
Akay [20] 2008	Rat	Effect of rhAPC on early phase of AP	Intra-ductal 5% sodium taurocholate	24 μg/kg/h as i.v. bolus starting 4 h after induction of AP	Laparotomy only AP AP + drotrecogin		9 h

3.2. Human recombinant activated protein C in clinical acute pancreatitis

The APCAP study comprised a pilot, double blind, randomized placebo-controlled trial (RCT) of intravenous infusion of rhAPC at a fixed dose of 24 μg/kg/h for 96 h in patients with SAP [22]. The inclusion criteria were appropriately focused to deliver a target population with severe disease: <96 h from onset of pain and at least one organ dysfunction (defined as organ specific Sequential Organ Failure Assessment (SOFA) score of at least 3 or 4, within 48 h of onset of the first organ dysfunction).

The *a priori* primary endpoint was a three-point difference in change of SOFA score with the authors predicting that this difference could be detected with a sample size of 32 patients were randomized and 16 patients comprised the intervention group. Baseline characteristics were similar and the mean ± standard deviation Acute Physiological and Chronic Health Evaluation II (APACHE II) score in the rhAPC group was 17.6 ± 8.5.

Their results showed no significant bleeding events. The 30-day mortality in the rhAPC group was 3 (19%) compared to 0 in the placebo group. The primary endpoint was not met and there was no significant difference in SOFA score. An interesting observation was that treatment with rhAPC was associated with an increase in serum levels of both total and conjugated bilirubin. There were no differences in ventilator-free days, in renal replacement therapy-free days, in vasopressor-free days or in days alive outside the hospital.

In addition to this principal randomized trial, there are case report-level experiences of the use of rhAPC in severe acute pancreatitis. The first documented report of rhAPC use in severe acute pancreatitis was by Machala and colleagues who reported their experience with 2 patients with infected pancreatic necrosis [23]. In 2006, Grochowiecki and colleagues published

Table 2
Principal endpoints of studies evaluating Human recombinant activated protein C in experimental acute pancreatitis. rhAPC = Human recombinant Activated Protein C; AP = Acute pancreatitis; TNF-α = Tumor necrosis factor alpha; IL-6 = Interleukin-6; MPO = Myeloperoxidase; MAPK = mitogen-activated protein kinases; mRNA = messenger ribonucleic acid; JNK = c-Jun N-terminal Kinases; ERK 1/2 = Extracellular signal-regulated Kinases.

First author	Study	Principal endpoints
Yamanel [18]	Effect of rhAPC on AP.	rhAPC associated with marked reduction in pancreatic edema, necrosis without increase in hemorrhage. rhAPC ameliorated serum amylase, TNF-α and IL-6. rhAPC associated with a reduction in bacterial translocation to mesenteric nodes.
Alsfasser [17]	Safety assessment.	Concentration-dependent thrombocytopenia. No evidence of bleeding.
Alsfasser [17]	Treatment of severe AP.	No difference in histologic scores of necrosis and edema. Significant reduction in pancreatic and pulmonary MPO.
Alsfasser [17]	rhAPC and survival.	6 of 7 (86%) survival in rhAPC group 3 of 8 (38%) in AP group.
Chen [19]	Effect of rhAPC on MAPK.	rhAPC-treatment resulted in reduction of histological evidence of pancreatic injury. rhAPC-treatment was associated with decreased gene, mRNA and protein expression of p38 MAPK and JNK with increased expression of ERK1/2. rhAPC-treatment resulted in lower histological scores of pancreatic injury (including necrosis).
Akay [20]	Effect of rhAPC on early phase of acute pancreatitis.	Mean serum amylase lower in treatment group. No difference in histopathologic scores of injury. No difference in pancreatic MPO activity. No difference in serum interleukin-6 concentrations.

a report detailing their experience with human recombinant activated protein C in the treatment of a patient with pancreatitis following the receipt of a transplanted pancreas [24]. Rybicki and colleagues report a further case treated with rhAPC because of rapidly progressive multiple organ failure [25]. All case reports describe a favorable outcome with no evidence of treatment-related hemorrhage but clearly provide only limited evidence.

4. Discussion

This report assesses the evidence for the evaluation of rhAPC as a disease modifying drug in acute pancreatitis. As with almost all other proposed disease modifying drugs, a body of evidence has accrued from studies in experimental acute pancreatitis. Placed together, rather than read in isolation, the relative similarities and disparities of protocol design become readily evident (Tables 1 and 2). The four studies featured here all use the rat model of intraductal sodium taurocholate infusion. An advantage of this model is its reproducibility and the resultant severe acute necrotizing pancreatitis [26]. A theoretical disadvantage is the physical manipulation of the pancreas in relation to assessment of an intervention, which has pancreatic hemorrhage as a potential side effect. The concentration of rhAPC used in the intervention groups and critically, the timing of intervention, vary considerably between studies. We have previously reported that studies of experimental acute pancreatitis can be broadly dichotomized into those that examine mechanistic components of the pancreatic inflammatory process and those that evaluate a potential specific therapy [27]. In this regard, the Alsfasser study [17] is well-designed and executed and reports a composite of a series of studies and is the sole experimental study to evaluate the effect of rhAPC on mortality. As such, although there is no formal process of weighting the importance of experimental studies, the Alsfasser study [17] findings carry considerable importance and their key finding of a reduction in mortality from 86% in the AP group to 38% in the AP group treated with rhAPC (at that time termed Drotrecogin Alfa) without evidence of bleeding is noteworthy. The failure to modify the histological features of pancreatic injury raises the possibility that beneficial effects of rhAPC are from actions out with the pancreas. The studies of Yamanel [18] and Chen [19] are broadly supportive of Alsfasser's findings [17]. Yamanel's [18] work contrasts with Alsfasser's [17] in demonstrating histological evidence of amelioration of pancreatic injury in animals with AP treated with rhAPC.

The findings of the Akay [20] study, which had intervention with rhAPC at 4 h in a 9 h protocol, reported no beneficial effect. This apparent disparity may relate to the relatively late timing of intervention in a model with a compressed time course. The studies of rhAPC in experimental acute pancreatitis can be summated as showing no evidence of pancreatic or remote hemorrhage as a consequence of treatment with 3 of 4 studies showing an amelioration of pancreatic injury as a consequence of the intervention. The Alsfasser study [17] provides key evidence of reduction in mortality with treatment and taken together this body of experimental evidence justifies progression to clinical evaluation of rhAPC as a specific disease modifying drug in SAP.

A particular interest with rhAPC is the interaction between its anticoagulant role and its anti-inflammatory properties. In the Alsfasser study, there were significant anti-inflammatory properties manifest by a reduction in myeloperoxidase [17]. Chen and colleagues also demonstrated a reduction in pro-inflammatory cytokines [21]. At the present time, there are insufficient data to differentiate with certainty whether the beneficial effects of rhAPC in experimental acute pancreatitis are effected predominantly by modulation of microvascular thrombosis, down regulation of inflammation or a combination of both.

This off license role of the drug was evaluated in a well-designed and well-executed study undertaken by the Helsinki group (APCAP [22]). Set against a contemporary backdrop of imminent re-categorization of the terminology around the severity of acute pancreatitis, the Kemppainen [22] study clearly identifies a cohort of patients with clinically severe acute pancreatitis (16 patients in the intervention arm had an APACHE II score of 17.6 ± 8.5 and a median age of 47 ± 8 years). They clearly learned the lesson of the lexipafant intervention study [28] and avoided recruiting a population where there was a disproportionate influence of the chronic health evaluation component of the APACHE II score. APCAP is also realistic and reasonable in looking for reduction in organ failure score as a primary endpoint rather than an effect on mortality. The problem with small group intervention studies is that a single adverse outcome (such as death after laparotomy) will have a disproportionate skewing effect on interpretation of endpoints. As such, we would concur completely with the Kemppainen [22] group's own conclusion that their study showed no serious hemorrhagic events associated with intervention but also no evidence of treatment-induced modification in the evolution of organ dysfunction. However, with a treatment arm of just 16 patients, this question clearly remains unanswered.

Little substantial additional information derives from the other anecdotal case reports.

The logical question to answer in progressing the assessment of rhAPC is whether the position of clinical equipoise in relation to intervention has been reached, currently exists or has passed. In this context, the experimental evidence clearly makes a case for evaluation and the carefully executed Kemppainen [22] study takes the body of evidence forward but the nature of its negative result means that currently, equipoise has not been reached. Put in the context of the important moral aspect of contemporary trial design, it remains unethical to randomize large numbers of patients with SAP to receive rhAPC in an intervention arm, in the absence of sufficient clinical evidence to justify altering any given individual's treatment from standard care.

However, a rational argument can be made for a smaller, randomized, placebo-controlled evaluation of rhAPC in SAP. As with APCAP [22], the definition of severity must provide information on APACHE II score, disease duration, organ dysfunction and systemic inflammatory response as these allow later workers to categorize the severity of the disease. Although doses in excess of 24 μg/kg/h may be of interest, as anti-inflammatory activity appears to be dose related, the weight of clinical safety data related to the sepsis treatment dose suggests that any higher concentration could not readily be justified.

Critical issues remain around primary endpoint and power calculation. In a placebo-controlled evaluation of a drug with complex, whole-organ, anti-inflammatory effects, a meaningful endpoint could be reduction in critical care occupancy. Given the negative findings of the APCAP [22] study, it is probably unwise to construct a power calculation on the Alsfasser [17] findings and a pragmatic compromise based on recruitment rates is realistic (bearing in mind that the APCAP investigators screened 215 patients to recruit 32). A practical primary endpoint would be reduction in critical care occupancy.

In conclusion, the experimental evidence underlying a potential role for rhAPC as a specific disease modifying drug in acute pancreatitis makes a strong but not conclusive case for evaluation. Set in the context of the lexipafant studies of the 1990s [29–32], the experimental evidence is probably stronger for rhAPC than existed for lexipafant. The single clinical randomized trial [22] strikes an important cautionary note as it is both well-designed and well-

executed. Set against a background of the knowledge of the increasing complexity of the biology of clinical sepsis and the continuing uncertainty over the clinical validity of rhAPC, the point of equipoise to justify a major randomized trial has not been reached. Yet, the Alsfasser [17] evidence remains important and the prospect of a specific disease modifying drug with anti-inflammatory actions and a role in preservation of microvascular patency cannot be ignored.

As a result of the negative outcome of the current PROWESS SHOCK study, rhAPC has currently been withdrawn from clinical use (Eli Lilly – personal communication). The withdrawal was made on the grounds of lack of efficacy in overwhelming sepsis rather than on safety grounds thus disease-specific evaluation in a setting such as severe acute pancreatitis remains an option. Further clinical evaluation is justified and supported by the evidence summated in this report.

Financial support

AKS has received financial support from Eli Lilly, Indianapolis USA for the XIGAP-1 study.

References

[1] Bradley E. A clinically based classification system for acute pancreatitis. Summary of the international symposium on acute pancreatitis, Atlanta, GA, September 11 through 13, 1992. Arch Surg 1993;128:586–90.
[2] Working Party of the British Society of Gastroenterology, Association of Surgeons of Great Britain and Ireland, Pancreatic Society of Great Britain and Ireland, Association of Upper GI Surgeons of Great Britain and Ireland. UK guidelines for the management of acute pancreatitis. Gut 2005;54(Suppl. 3): iii1–9.
[3] Banks P, Freeman M. Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006;101:2379–400.
[4] Bassi C, Falconi M, Talamini G, Uomo G, Papaccio G, Dervenis C, et al. Controlled clinical trial of pefloxacin versus imipenem in severe acute pancreatitis. Gastroenterology 1998;115:1513–7.
[5] Sainio V, Kemppainen E, Puolakkainen P, Taavitsainen M, Kivisaari L, Valtonen V, et al. Early antibiotic treatment in acute necrotising pancreatitis. Lancet 1995;346:663–7.
[6] Isenmann R, Rünzi M, Kron M, Kahl S, Kraus D, Jung N, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. Gastroenterology 2004;126: 997–1004.
[7] Petrov MS, Loveday BP, Pylypchuk RD, McIlroy K, Phillips AR, Windsor JA. Systematic review and meta-analysis of enteral nutrition formulations in acute pancreatitis. Br J Surg 2009;96:1243–52.
[8] Powell JJ, Murchison JT, Fearon KC, Ross JA, Siriwardena AK. Randomized controlled trial of the effect of early enteral nutrition on markers of the inflammatory response in predicted severe acute pancreatitis. Br J Surg 2000; 87:1375–81.
[9] Nitsche R, Folsch UR. Role of ERCP and endoscopic sphincterotomy in acute pancreatitis. Baillieres Best Pract Res Clin Gastroenterol 1999;13:331–43.
[10] Tsiotos G, Luque-de Leon E, Sarr M. Long-term outcome of necrotizing pancreatitis treated by necrosectomy. Br J Surg 1998;85:1650–3.
[11] Will U, Wegener C, Graf K, Wanzar I, Manger T, Meyer F. Differential treatment and early outcome in the interventional endoscopic management of pancreatic pseudocysts in 27 patients. World J Gastroenterol 2006;12: 4175–8.
[12] Esmon CT. Crosstalk between inflammation and thrombosis. Maturitas 2004; 47:305–14.
[13] Zeerleder S, Hack CE, Wuillemin WA. Disseminated intravascular coagulation in sepsis. Chest 2005;128:2864–75.
[14] Esmon CT. Protein C anticoagulant pathway and its role in controlling microvascular thrombosis and inflammation. Crit Care Med 2001;29:S48–51 [discussion 51–42].
[15] Taylor Jr FB, Chang A, Esmon CT, D'Angelo A, Vigano-D'Angelo S, Blick KE. Protein C prevents the coagulopathic and lethal effects of *Escherichia coli* infusion in the baboon. J Clin Invest 1987;79:918–25.
[16] Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, et al. Efficacy and safety of recombinant human activated protein c for severe sepsis. N Engl J Med 2001;344:699–709.
[17] Alsfasser G, Warshaw AL, Thayer SP, Antoniu B, Laposata M, Lewandrowski KB, et al. Decreased inflammation and improved survival with recombinant human activated protein C treatment in experimental acute pancreatitis. Arch Surg 2006;141:670–6.
[18] Yamanel L, Yamenel L, Mas MR, Comert B, Isik AT, Aydin S, et al. The effect of activated protein C on experimental acute necrotizing pancreatitis. Crit Care 2005;9:R184–90.
[19] Chen P, Zhang Y, Qiao M, Yuan Y. Activated protein C, an anticoagulant polypeptide, ameliorates severe acute pancreatitis via regulation of mitogen-activated protein kinases. J Gastroenterol 2007;42:887–96.
[20] Akay S, Ozutemiz O, Yenisey C, Genc Simsek N, Yuce G, Batur Y. Use of activated protein C has no avail in the early phase of acute pancreatitis. HPB (Oxford) 2008;10:459–63.
[21] Ping C, Yongping Z, Minmin Q, Weiyan Y, Yaozong Y. Activated protein C improves the severity of severe acute pancreatitis via up-regulating the expressions of endothelial cell protein C receptor and thrombomodulin. Dig Dis Sci 2010;55:1599–609.
[22] Pettilä V, Kyhälä L, Kylänpää M-L, Leppäniemi A, Tallgren M, Markkola A, et al. APCAP – activated protein C in acute pancreatitis: a double-blind randomized human pilot trial. Crit Care 2010;14. R139–R137.
[23] Machala W, Wachowicz N, Komorowska A, Gaszynski W. The use of drotrecogin alfa (activated) in severe sepsis during acute pancreatitis – two case studies. Med Sci Monit 2004;10:CS31–6.
[24] Grochowiecki T, Nazarewski S, Meszaros J, Kanski A, Wojtaszek M, Kosinski C, et al. Use of drotrecogin alpha (recombinant human activated protein C, rhAPC) in the treatment of severe sepsis induced by graft pancreatitis after simultaneous pancreas and kidney transplantation: a case report. Transplant Proc 2006;38:276–9.
[25] Rybicki Z, Truszczynski A, Skibinski M. Recombinant human activated protein C administered twice to the same patient with shock caused by the acute pancreatitis and with septic shock as iatrogenic complication. Pol Przegl Chir 2007;79:80–6.
[26] Case RM. Is the rat pancreas an appropriate model of the human pancreas? Pancreatology 2006;6:180–90.
[27] Mason JM, Siriwardena AK. Designing future trials in acute pancreatitis. Pancreatology 2005;5:113–5.
[28] Johnson CD, Kingsnorth AN, Imrie CW, McMahon MJ, Neoptolemos JP, McKay C, et al. Double blind, randomised, placebo controlled study of a platelet activating factor antagonist, lexipafant, in the treatment and prevention of organ failure in predicted severe acute pancreatitis. Gut 2001; 48:62–9.
[29] Zhou W, Levine BA, Olson MS. Platelet-activating factor: a mediator of pancreatic inflammation during cerulein hyperstimulation. Am J Pathol 1993; 142:1504–12.
[30] Leonhardt U, Fayyazzi A, Seidensticker F, Stockmann F, Soling HD, Creutzfeldt W. Influence of a platelet-activating factor antagonist on severe pancreatitis in two experimental models. Int J Pancreatol 1992;12:161–6.
[31] Formela LJ, Wood LM, Whittaker M, Kingsnorth AN. Amelioration of experimental acute pancreatitis with a potent platelet-activating factor antagonist. Br J Surg 1994;81:1783–5.
[32] Albert DH, Conway RG, Magoc TJ, Tapang P, Rhein DA, Luo G, et al. Properties of ABT-299, a prodrug of A-85783, a highly potent platelet activating factor receptor antagonist. J Pharmacol Exp Ther 1996;277:1595–606.