ORIGINAL ARTICLE

Etanercept, a TNF-alpha Binding Agent, Is Ineffective in the Prevention of Post-ERCP Pancreatitis in Canines

Jonathan M Buscaglia[1], Brian W Simons[2], Brent J Prosser[1], Dawn S Ruben[2], Samuel A Giday[1], Priscilla Magno[1], John O Clarke[1], Eun Ji Shin[1], Anthony N Kalloo[1], Sergey V Kantsevoy[1], Kathleen L Gabrielson[2], Sanjay B Jagannath[1]

[1]Division of Gastroenterology and Hepatology and [2]Department of Molecular and Comparative Pathobiology, Johns Hopkins University School of Medicine, Johns Hopkins Hospital. Baltimore, MD, USA

ABSTRACT

Context The incidence of post-ERCP pancreatitis is 1-22%. It continues to be a difficult problem for endoscopist and patient. Uncovering an agent that may be used to prevent its occurrence is critical.

Objective The aim of our study was to investigate the role of etanercept in the prevention of post-ERCP pancreatitis.

Design Endoscopic retrograde pancreatography (ERP)-induced injury was performed in dogs using a previously established endoscopic model of post-ERCP pancreatitis.

Animals Eight study dogs underwent ERP: 4 were pre-treated with etanercept one day before the procedure and 4 were untreated. In addition, three control dogs not undergoing ERP were also studied.

Main outcome measures Serum levels of amylase, lipase, and TNF-alpha, as well as the ratio of urinary trypsinogen activation peptide (TAP) and urinary creatinine, were measured before and after ERP. Necropsy was performed on post-operative day 5. All pancreatic specimens were graded by two blinded pathologists according to a validated scoring system.

Results Eight study dogs developed mild to moderate clinical pancreatitis with hyperamylasemia (11,538±4,065 U/L *vs.* 701±157 U/L; post-ERP peak levels *vs.* baseline values: P<0.001) and hyperlipasemia (3,637±2,333 U/L *vs.* 246±125 U/L; P=0.003). Mean total injury score was significantly elevated in study dogs compared to control dogs (6.16±1.85 *vs.* 1.06±0.49; P=0.001). There were escalating total injury scores concordant with more elaborate methods of endoscopically-induced injury although the trend did not reach the statistical significance (P=0.223). When comparing untreated to etanercept-treated dogs, there were no significant differences in serum amylase levels (P=0.903), serum lipase levels (P=0.771), TAP/creatinine urinary ratio (P=0.912), and pancreatic injury score (P=0.324).

Conclusion Etanercept is ineffective in prevention of mild to moderate post-ERCP pancreatitis in canines. ERP-induced pancreatic injury can be used as a reliable animal model for studies investigating therapy and prevention of post-ERCP pancreatitis.

INTRODUCTION

Since the inception of endoscopic retrograde cholangiopancreatography (ERCP) in the early 1970's, physicians have described the unfortunate complication of pancreatitis following this procedure [1]. Although it occurs in the minority of patients, it is completely iatrogenic, and it may cause significant morbidity, or even mortality [2]. Post-ERCP pancreatitis is said to occur in approximately 1-22% of all cases, yet in some patient populations that are at high-risk, its incidence may be as high as 20-30% [3].

In acute pancreatitis, the activation of inflammatory cells with the release of cytokines plays an important role in the disease process [4]. Several studies have demonstrated the unique characteristics of different mediators such as interleukin-6 (IL-6), IL-8, and IL-10 [5, 6, 7, 8]. The significance of tumor necrosis factor (TNF) in acute pancreatitis, however, is less well-established. Although some have shown the concentration of soluble TNF receptors to correlate with disease severity [9], others have found significant levels in only the early stages of severe acute pancreatitis [10]. In a rat model of acute pancreatitis, the chimeric TNF antibody, infliximab, was found to significantly decrease serum amylase activity and pancreas histopathologic scores [11]. More recently, etanercept (a soluble TNF-alpha binding agent) has been shown to attenuate the development of acute pancreatitis in a murine model of disease [12]. The primary aim of our study was to investigate the role of etanercept in the prevention post-ERCP pancreatitis using a previously established endoscopic model of disease in canines [13]. The secondary aim was to ascertain levels of TNF-alpha in mild to moderate acute pancreatitis resulting from ERCP.

MATERIALS AND METHODS

Pre-Procedure

We performed endoscopic retrograde pancreatography (ERP) procedures on eight consecutive male 25-35 kg hound dogs (*Canis familiaris*). Animals undergoing ERP were divided into one of two categories: untreated group and treatment group. Those assigned to the treatment group received etanercept (Amgen Co., Thousand Oaks, CA, USA) at a dose of 1 mg/kg administered subcutaneously dorsal to the scapula one day prior to the procedure. Those dogs in the untreated group did not receive any injection before ERP.

Twenty-four hours prior to the procedure, all dogs were fed a standard canine lab diet and allowed free access to water. Twelve hours prior to the procedure, all solid food was held. On the morning of the ERP, pre-anesthesia medication was administered consisting of an intramuscular injection of 0.03 mg/kg acepromazine (10 mg/mL; Fort Dodge Inc., Ames, IA, USA). Thirty minutes later an intravenous catheter was placed in the foreleg cephalic vein of each dog, and the following was administered: 100 mg/mL Telazol (tiletamine HCl plus zolazepam HCl; Leerle Parenterals Inc., Carolina, Puerto Rico) reconstituted with 2.5 mL of 100 mg/mL ketamine HCl and 2.5 mL of 100 mg/mL xylazine at a total dose of 0.02 mL/kg. All procedures were performed under 1.5% to 2.0% isoflurane general anesthesia with endotracheal intubation.

Once on the operating table, all animals had continuous monitoring of end tidal carbon dioxide, peripheral pulse and oxygen saturation by pulse oximetry. A standard 8-F Foley catheter was inserted through the urethra and into the bladder. After the internal balloon was inflated with 3 mL of water, the external end and stop-cock portions of the catheter were sutured in place to the dog's skin surface. Baseline urine was collected, and blood samples were drawn from the internal jugular vein. All animals were given 0.9% NaCl saline solution throughout the procedure.

Procedure

A standard overtube (Olympus Optical Co. Ltd., Tokyo, Japan) was advanced into the dog's stomach with a standard upper endoscope (GIF-160, Olympus Optical Co. Ltd., Tokyo, Japan) inside the tube. All

remaining gastric contents were adequately suctioned out through the endoscope. Once the tip of the overtube was positioned in the distal esophagus, the endoscope was withdrawn. A regular, adult size, side-viewing duodenoscope (TJF-160, Olympus Optical Co. Ltd., Tokyo, Japan) was then advanced down through the pylorus and into the proximal intestine. The intestinal mucosa was scanned in order to locate the minor duodenal papilla. The minor papilla serves as the main duct of drainage in the canine pancreas. The more proximal major papilla acts as an accessory drainage duct, and it joins the bile duct prior to emptying into the duodenal lumen [14].

After locating the minor papilla, a standard 7-F endoscopic sphincterotome (Tri-tome®, Cook Endoscopy, Winston-Salem, NC, USA) loaded with a 0.035-inch guidewire (Jagwire®, Boston Scientific Corp., Natick, MA, USA) was used to cannulate the papillary orifice. Following cannulation, 1-2 mL of contrast (Omnipaque®, Amersham Health, Princeton, NJ, USA) was injected into the pancreatic duct in order to confirm proper position. Once successful access to the pancreatic duct was obtained, ERP was performed in one of four manners based on our previously established endoscopic model of disease [13]. Method 1: pancreatic duct acinarization with 20 mL of contrast; method 2: pancreatic duct acinarization with 30 mL of contrast; method 3: pancreatic duct acinarization with 30 mL of contrast, plus 5-minute balloon occlusion of the papillary orifice, plus endoscopic pancreatic sphincterotomy; method 4: pancreatic duct acinarization with 30 mL of contrast, plus injection of 3 g of ursodeoxycholic acid (powder) mixed in 10 mL of sterile water, plus 5-minute balloon occlusion of the papillary orifice, plus endoscopic pancreatic sphincterotomy. Balloon occlusion was performed with a 6 mm biliary dilating balloon (Bard Inc., Covington, GA, USA) in all cases. Sphincterotomy was performed using 40 W blended current electrocautery (Valley Lab-Electrosurgery Unit, Tyco Corp., Boulder, CO, USA).

Following ERP all dogs were extubated and allowed to recover from anesthesia in their own cages. They were examined at regular intervals by a member of the veterinary staff and assessed for pain or evidence of procedure-related complications. Analgesic medicine for animal discomfort was administered at the discretion of the examining staff member.

All dogs were sacrificed for necropsy on post-operative day 5, or sooner if clinical symptoms of pancreatitis were felt to be severe or inhumane.

Controls

Three identical species dogs that did not undergo ERP, abdominal intervention, or etanercept injection were euthanized, and their pancreas was obtained at necropsy to serve as controls. Control dogs were used in other animal institutional review board-approved trials involving non-GI protocols. Serum and urine were not collected in control dogs.

Sample Collection

Urine samples were aspirated from the urinary catheter of each dog in order to measure trypsinogen activation peptide (TAP; nM) (TAP Assays, Biotrin Inc., Dublin, Ireland) levels and urine creatinine (mg/dL) levels (Antech Diagnostics, Lake Success, NY, USA). Samples were collected at baseline, immediately following ERP, and then 30 min, 3 h, 6 h, and 12 h post-procedure. The dog's bladder was completely emptied after each sample was obtained. Individual urinary TAP levels (nM) were divided by the corresponding urine creatinine level (mg/dL) in order to obtain the urinary TAP/creatinine ratio. The peak urinary TAP/creatinine values of the five samples collected after ERP were recorded in each dog.

Serum levels of amylase and lipase were also measured (Antech Diagnostics, Lake Success, NY, USA). Samples were obtained at baseline and 2 h post-procedure. Additional samples were collected on days 1, 2, and 5 following ERP. The peak amylase and lipase values of

the four samples collected after ERP were recorded in each dog.

Cytokine Analysis

Serum samples for TNF-alpha measurement were obtained at the identical time intervals as amylase and lipase. Blood was collected, centrifuged at 3,000 rpm for 15 minutes, aliquoted and stored in a -70°C freezer until analyzed. Serum levels of canine TNF-alpha were determined using a commercially available EIA kit (R&D Systems, Minneapolis, MN, USA). Serum samples were tested in duplicate according to the manufacture's instructions. The plates were read immediately after application of the stop solution. The optical density of each sample was determined using VERSAmax® tunable microplate reader (Molecular Devices, Sunnyvale, CA, USA). Results were calculated from a standard curve and reported accordingly in pg/mL. The minimum detectable dose for TNF-alpha is 2.4 pg/mL.

Histology

Following euthanasia, the pancreas was resected and fixed in 10% buffered formalin. The pancreas was systematically divided into six transverse sections representing the following areas: distal left lobe, proximal left lobe, body of the pancreas at the major papilla, body of the pancreas at the minor papilla, proximal right lobe, and distal right lobe. The sections underwent routine histological processing, stained with hematoxylin and eosin, and evaluated with light microscopy by two pathologists in tandem who were blinded to the treatment arm for each dog. Each section was scored for eight different categories of pancreatic injury: neutrophilic inflammation, mononuclear inflammation, acinar cell necrosis, fibrosis, acinar cell atrophy, fat necrosis, edema, and hemorrhage. A previously described and validated pathologic scoring system [15] was used with the following modifications: acinar cell necrosis was defined as necrosis of individual acinar cells, and mononuclear inflammation was defined as the presence of lymphocytes, plasma cells, or macrophages within the pancreatic parenchyma or peri-pancreatic tissue. The severity of the lesions was graded on a scale of 0 to 4 using a modification of the previous scoring system [15]. Severity scores were defined as: grade 0 (lesion absent); grade 1 (less than 10% of the section affected); grade 2 (10-33% of the section affected); grade 3 (33-66% of the section affected); grade 4 (more than 66% of the section affected). In all dogs, the severity scores (0-4) in each of the six transverse slide sections were used to calculate an average value for the eight different categories of pancreatic injury. These eight values were then summed to calculate the total pancreatic injury score for each dog.

ETHICS

The study was approved by the Johns Hopkins University Animal Care and Use Committee and Institutional Review Board. It met all federal guidelines for the humane use and treatment of animals according to the "Guide for the Care and Use of Laboratory Animals (1996)", prepared by the National Academy of Sciences. A review committee was implemented to monitor data acquisition and animal safety. There were no violations in safety guidelines or the approved protocol plan.

STATISTICS

Data are shown as mean and standard deviation (SD). Peak serum amylase and lipase activities, as well as peak TAP/creatinine urinary ratio, were compared to baseline values by using the paired t-test. The differences in these peak values between the untreated and the treated group were analyzed using the unpaired t-test.

The eight different scores of pancreatic injury, as well as the total injury score, in the eight dogs that underwent ERP were compared to the control dogs using the unpaired t-test. Similar comparisons were made between the four untreated and the four etanercept-treated dogs.
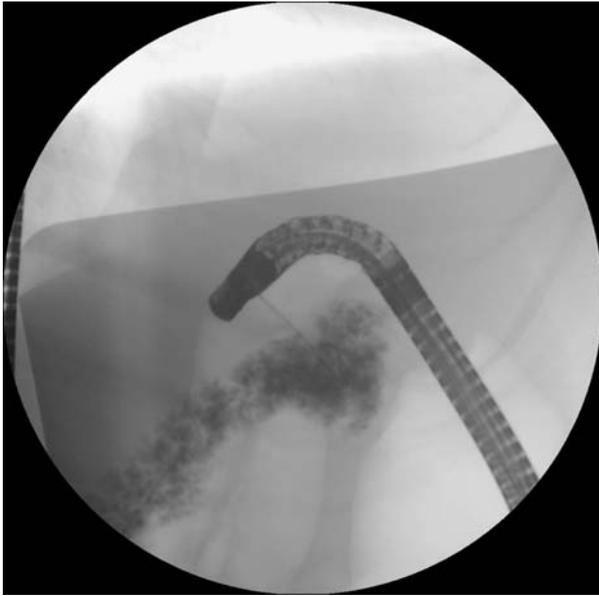
Figure 1. Fluoroscopic image demonstrating acinarization of the pancreatic duct by endoscopic retrograde pancreatography.

The one-way linear term ANOVA was applied to test the relationship between the total injury score and the severity of endoscopic approach (ERP method). Data were analyzed by using the VassarStats web site (http://faculty.vassar.edu/lowry/VassarStats.html).In all analyses, a two-tailed P value of less than 0.05 was considered to be statistically significant.

RESULTS

A total of eight survival experiments were performed. Selective cannulation of the minor papilla was successful in all animals.

Pancreatic duct acinarization was achieved in each dog (Figure 1). There were no significant alterations in the animals' vital signs during the procedures (data not shown). There were no peri-procedural complications such as bleeding, perforation, infection, etc. Each animal was recovered uneventfully from anesthesia following ERP. Seven animals were sacrificed for necropsy on post-operative day 5, as planned, while the dog of the untreated group operated with ERP method 4 had severe clinical pancreatitis with associated fever, tachycardia, vomiting, hypotension, and renal dysfunction. This animal was euthanized on post-operative day 2.

Figure 2 demonstrates the changes in amylase and lipase levels before and after ERP in all eight study dogs. Peak amylase levels were significantly increased compared to baseline values registered before the procedure (11,538±4,065 U/L *vs.* 701±157 U/L; P<0.001). Peak lipase levels were also elevated following ERP, and the difference reached statistical significance (3,637±2,333 U/L *vs.* 246±125 U/L; P=0.003). When comparing peak pancreatic enzyme levels amongst untreated and etanercept-treated dogs, however, there were no significant differences in those dogs that received etanercept prior to ERP (Figure 3). For amylase levels, the mean value in the untreated group was 11,735±4,596 U/L *vs.* 11,341±4,162 U/L in the treatment group (P=0.903). For lipase levels, the value in the

Figure 2. Mean (±SD) peak serum amylase and lipase levels compared to baseline in all eight study dogs.
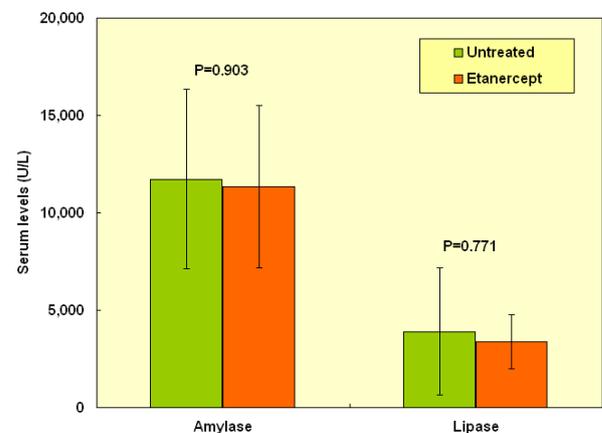

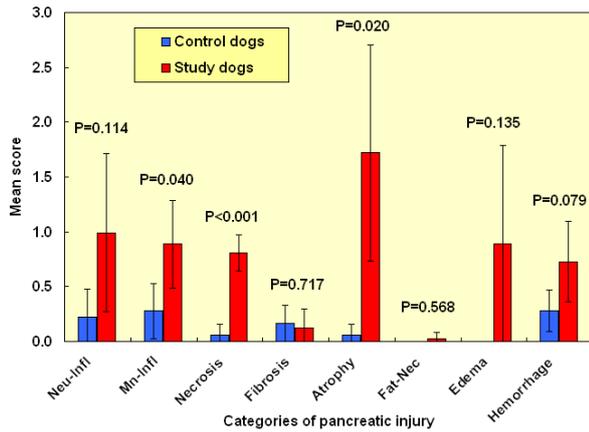**Figure 3.** Mean (±SD) peak serum amylase and lipase levels in untreated and etanercept-treated dogs.

Figure 4. Mean (±SD) pancreatic injury scores for the three control dogs and all eight study dogs. (Neu-Infl: neutrophilic inflammation; Mn-Infl: mononuclear inflammation; Fat-Nec: fat necrosis).

untreated group was 3,906±3,253 U/L *vs.* 3,368±1,389 U/L in the treatment group (P=0.771).

Mean peak TAP/creatinine urinary ratio was compared to the corresponding baseline value in all eight animals. Although peak values were greater than baseline values (0.71±0.64 *vs.*0.23±0.17), this difference was not statistically significant (P=0.097). There was no significant difference in peak TAP/creatinine urinary ratio between the four untreated dogs and the four etanercept-treated ones (0.74±0.71 *vs.* 0.68±0.76, respectively; P=0.910).

Histology

The mean total injury score for the study dogs was 6.16±1.85 *vs.* 1.06±0.49 for the control dogs (P=0.001). When compared to the three control dogs, the eight study dogs had an elevated injury score in all histological categories except for fibrosis (Figure 4). Mononuclear inflammation (P=0.040), acinar cell necrosis (P<0.001), and atrophy (P=0.020) were all significantly worse in the study dogs. Figure 5 highlights some of the
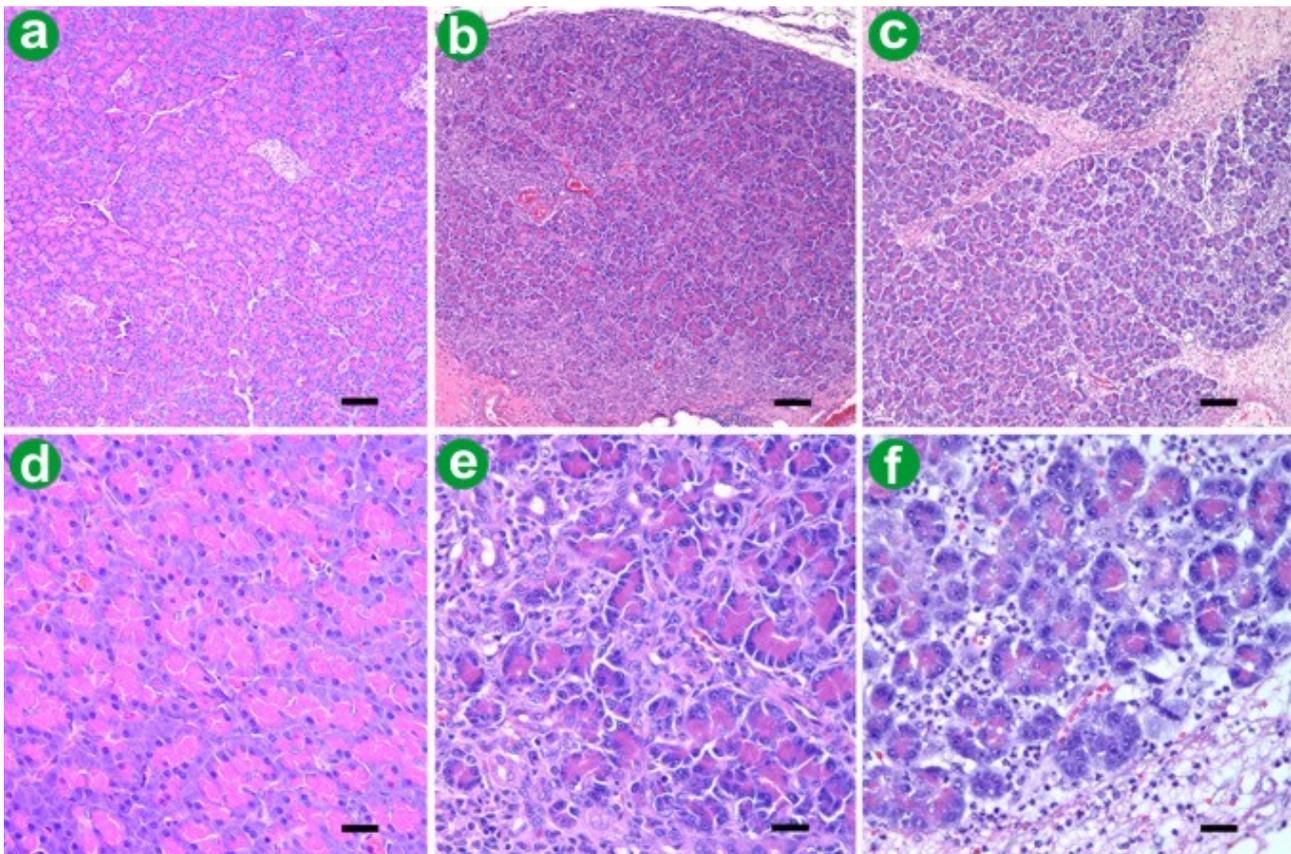

Figure 5. Histological analysis of the pathology in the pancreas specimens of control dogs and study (ERP) dogs. **a-f.** Hematoxylin-eosin staining of pancreatic sections. **a,d.** Control dog pancreas showing normal lobular architecture with tightly associated acinar cells. **b,e.** Representative sections of the pancreas (dog of the untreated group, method 1) showing mild leukocytic infiltration and acinar cell atrophy. **c,f.** Representative sections of the pancreas (dog of the untreated group, method 4) showing inter- and intra-lobular edema, and marked acute inflammation. (Scale bar in **a,b,c**: 100 µm; scale bar in **d,e,f**: 25 µm).
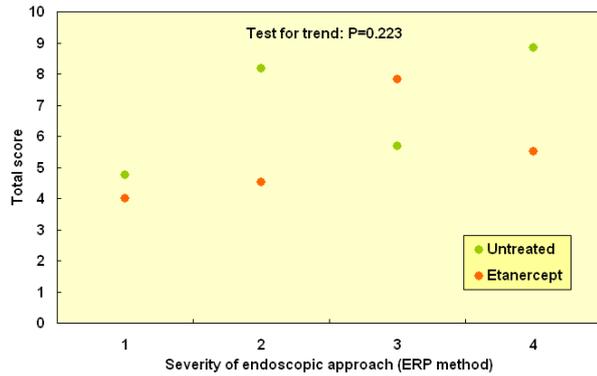
Figure 6. Total pancreatic injury scores in the eight study dogs according to the four different methods of endoscopic injury. (Method 1: pancreatic duct acinarization with 20 mL of contrast; method 2: pancreatic duct acinarization with 30 mL of contrast; method 3: pancreatic duct acinarization with 30 mL of contrast, plus 5-minute balloon occlusion of the papillary orifice, plus endoscopic pancreatic sphincterotomy; method 4: pancreatic duct acinarization with 30 mL of contrast, plus injection of 3 g of ursodeoxycholic acid (powder) mixed in 10 mL of sterile water, plus 5-minute balloon occlusion of the papillary orifice, plus endoscopic pancreatic sphincterotomy).

microscopic differences between control dogs and study dogs.

When the dogs were paired according to the method of ERP-induced injury, there were escalating total injury scores concordant with the severity of endoscopic approach (Figure 6). method 1 had the lowest total mean injury score (4.38), while method 4 registered the highest summed score (7.17) although the trend did not reach the statistical significance (P=0.223).

The total score for the untreated group was 6.86±1.95 *vs*. 5.47±1.70 in the treatment group (P=0.324). Individual pancreatic injury scores for the two groups of dogs are shown in Figure 7. There were no significant differences between the two groups of dogs in each of the eight different categories of histological injury.

Cytokine Analysis

TNF-alpha measurements were ascertained in all eight study dogs at each of the five collection intervals described above, except for the dog of the untreated group who was euthanized prior to the last serum sample collection due to severe clinical symptoms. In

this dog, as well as, in six of the other dogs, all collections yielded TNF-alpha concentrations below the minimal detectable level of 2.4 pg/mL. Only in the remaining dog (etanercept-treated; ERP method 4) there was a slight elevation of TNF-alpha in the duplicate samples recorded at post-procedure times 2 h (3.09±1.55 pg/mL) and day 2 (3.37±0.39 pg/mL), while all the other samples (baseline, day 1, and day 5) of this dog too had undetectable values.

DISCUSSION

Post-ERCP pancreatitis has been a serious and frustrating problem for endoscopists since the inception of ERCP in the early 1970's. It is relatively common complication that bears an incidence of roughly 1-22% [3]. In some patients who are considered high-risk for post-ERCP pancreatitis (e.g. female gender, suspected sphincter of Oddi dysfunction, or previous episode of post-ERCP pancreatitis), the incidence may be as high as 20-30% [3]. As a result, numerous pharmacological agents have been studied in an attempt to prevent or ameliorate this disease. Drugs such as gabexate, allopurinol, diclofenac, nifedipine, corticosteroids, somatostatin analogues, interleukin-10, and glyceryl trinitrate have all been previously evaluated with varying results [16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36].
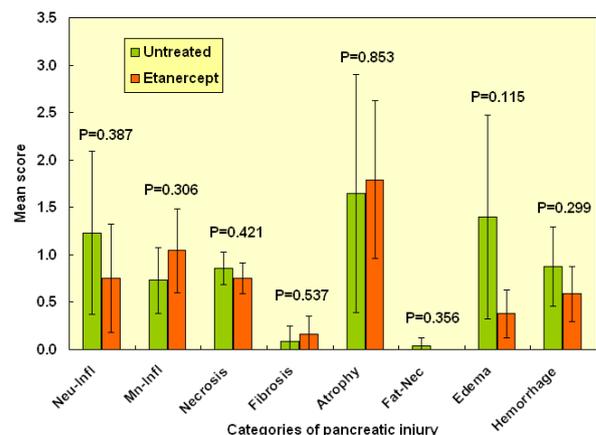

Figure 7. Mean (±SD) pancreatic injury scores for the four untreated dogs and the four etanercept-treated dogs.
Neu-Infl: neutrophilic inflammation
Mn-Infl: mononuclear inflammation
Fat-Nec: fat necrosis).

Theories as to how these agents may reduce the risk of post-ERCP pancreatitis include inhibition of premature intrapancreatic enzyme activation, reduction in sphincter of Oddi hypertension, and control of the inflammatory cascade [37].

In acute pancreatitis, the activation of inflammatory cells with the release of cytokines plays an important role in the disease process [4]. Studies have demonstrated a substantial rise in both interleukin-6 (IL-6) and IL-8 immediately following an episode of acute pancreatitis [5, 6]. Serum levels of these cytokines correlate with disease severity, and higher levels are seen in those patients with severe acute pancreatitis [4]. Conversely, IL-10 has been studied and shown to reduce the inflammatory response in acute pancreatitis. Deviere *et al.* demonstrated that a single intravenous dose of IL-10 given 30 minutes before an ERCP procedure independently reduces the risk of post-ERCP pancreatitis [7]. Furthermore, higher levels of IL-10 have been demonstrated in the sera of those patients with milder forms of the disease [4, 8].

Tumor necrosis factor-alpha (TNF-alpha) also plays a role in the pathogenesis of acute pancreatitis, but its part may be less well-defined compared to other cytokines. In a rat or mouse model of disease, TNF-alpha has been shown to be elevated in the sera of animals with experimentally-induced acute pancreatitis [38, 39, 40, 41]. Furthermore, TNF-alpha blocking agents, such as etanercept, have been shown to attenuate the disease process and even improve survival in some studies [12, 42]. In human studies, however, significantly elevated levels of TNF-alpha are seen only in the very early stages of severe acute pancreatitis [10].

Large animal models that study acute pancreatitis exist, but one that specifically mimics post-ERCP pancreatitis has not been fully developed. Prior studies that have attempted to create pancreatitis in large animals have done so by performing an open laparotomy with surgical duodenostomy and the injection of a caustic agent directly into the pancreatic duct. Sodium taurocholate, trypsin, or autologous bile are usually the agents of choice in these studies [2, 43, 44, 45]. The problem with these models is that they do not simulate what occurs inside the boundaries of a human ERCP. We have previously demonstrated that post-ERCP pancreatitis is effectively induced in dogs with increasing severity by acinarization of the pancreatic duct, with or without balloon-occlusion and sphincterotomy [13]. A similar model was utilized in the present study to provide the platform for investigating the role of etanercept in the prevention of ERCP-induced pancreatitis.

In the current study, we have effectively induced acute pancreatitis by means of ERP in eight consecutive animals, using four escalating endoscopic methods of inducing pancreatic injury. Post-ERCP pancreatitis was documented by a significant elevation in pancreatic enzyme levels, as well as a significant increase in the total histological pancreatic injury scores of all eight study dogs compared to three control dogs. The trend in severity of pancreatic injury correlated with the severity of endoscopic technique during ERP. That is, the necropsy specimens with the least amount of injury were seen in the dogs of method 1 (pancreatic duct acinarization with 20 mL of contrast), and the specimens with the greatest amount of injury were seen in the dogs of method 4 (acinarization with 30 mL of contrast, plus injection of 3 g of ursodeoxycholic acid, plus balloon occlusion of the papillary orifice, plus endoscopic pancreatic sphincterotomy).

Four of the eight dogs in this study were pre-treated with etanercept one day prior to their ERP procedure. This soluble TNF-alpha binding agent appeared to have no effect on the development of post-ERCP pancreatitis. Peak levels of serum pancreatic enzymes and urinary TAP/creatinine urinary ratio were similar among the two groups of dogs. In addition, when comparing necropsy specimens between the two groups, total pancreatic injury scores did not significantly differ from one another. Individual pancreatic injury scores were also similar in all categories of pathology.

Regarding the lack of efficacy of etanercept in this study, the near complete absence of detectable TNF-alpha in the sera of all eight study dogs must be weighed heavily. Ruaux *et al.* previously examined the plasma samples for TNF-alpha in 60 dogs with varying degrees of spontaneous acute pancreatitis [46]. TNF-alpha was detectable in only 6.7% (4/60) of dogs, and all four of these animals had severe acute pancreatitis with multi-organ system failure. Based on these results, and those of the present study, it appears as though additional factors may be involved in the release of TNF-alpha in acute pancreatitis. It may be that this cytokine asserts its effect only in the extreme end of disease severity. If so, this might explain the lack of detectable TNF-alpha in the eight dogs of this study; as all but one had mild to moderate ERCP-induced acute pancreatitis (one dog had severe disease). Without significant elevations in TNF-alpha levels (suggesting its importance in the pathogenesis of post-ERCP pancreatitis) it is difficult to imagine how a TNF-alpha binding agent such as etanercept could be used to limit disease severity.

Despite the lack of efficacy of etanercept in the prevention of canine post-ERCP pancreatitis, this study is unique and uncovers some important principles. First, it confirms the utilization of an endoscopically-based large animal model of post-ERCP pancreatitis. As procedure-related factors are known to play a significant role in post-ERCP pancreatitis, this model replicates the working conditions of a human ERCP, thus providing a platform that allows for safe, reliable investigation of maneuvers, devices, and future pharmacological agents that may reduce the occurrence of post-ERCP pancreatitis. Small-scale studies addressing different prophylactic agents of choice, or certain preventative endoscopic techniques, could be performed using this animal model before undertaking larger, human clinical trials. Secondly, this study yields further information regarding the role of TNF-alpha in acute pancreatitis. Based on our results, it seems as though TNF-alpha plays a small

role, if any, in the inflammatory cascade of mild to moderate acute disease. Therefore, agents blocking or inhibiting this cytokine will likely have little effect in this form of disease severity. On the other hand, TNF-alpha may play a significant role in severe acute pancreatitis as suggested in other studies [10], and future investigations of this sort should likely focus on the use of anti-TNF-alpha agents for the prevention of post-ERCP pancreatitis in cases of severe disease only.

In conclusion, etanercept, a TNF-alpha binding agent, is ineffective at preventing post-ERCP pancreatitis using a canine model of disease. TNF-alpha appears to have little role in the inflammatory cascade and pathogenesis of mild to moderate post-ERCP pancreatitis in canines. Nonetheless, this study confirms an endoscopically-based, large animal model of post-ERCP pancreatitis, and it serves as a platform for future studies evaluating this disease.

Correspondence

Jonathan M Buscaglia
Johns Hopkins Hospital
1830 E. Monument Street
Room 7100-A
Baltimore, MD 21205
USA
Phone: +1-443.287.7476
Fax: +1-410.955.2108
Mobile: +1-917.414.9290
E-mail: jbuscaglia@jhmi.edu

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