Response to Letter to the Editor "Design Flaws in Study of Prophylaxis of Postendoscopic Retrograde Cholangiopancreatography Pancreatitis" by Feng Liu et al

To the Editor:

We thank Jia-Su Li and Feng Liu for their interest in our article and critical review of its study design. We assumed an occurrence rate of postendoscopic retrograde cholangiopancreatography pancreatitis (PEP) of 2.5% to estimate the necessary sample size for our study. Because only limited data are available concerning PEP prophylaxis using 50 mg of rectal diclofenac, we assumed the PEP rate by referring to previous studies that had evaluated PEP prophylaxis using a temporary pancreatic stent in consecutive patients at Japanese high-volume centers. The occurrence rates of PEP were around 3% in patients who received prophylactic pancreatic stenting in those studies.[1,2] Our assumption of the PEP rate of 2.5% may be comparable to the results of those studies. If the use of 50 mg of rectal diclofenac was noneffective in PEP prophylaxis compared with pancreatic stenting, we might have been unable to show the equivalencies of PEP prophylaxis among 3 treatment groups.

Concerning the baseline characteristics of each group, there was no statistical difference in patient-related risk factors. There was also no statistical difference in procedure-related risk factors such as difficult cannulation (time >10 minutes), repetitive pancreatic guidewire passages, pancreatic injection, pancreatic sphincterotomy or precut sphincterotomy. However, there was a tendency to use a pancreatic guidewire technique for biliary cannulation more frequently in patients who had received prophylactic pancreatic stenting. Finally, there was no difference in the postprocedural management strategy of each group. All patients were hospitalized and received standard intravenous hydration (60–80 mL/h during and after the procedure) and prophylactic antibiotics. In this study, aggressive intravenous hydration was not used to compare the PEP prophylaxis directly among the 3 treatment groups.

We defined patients at high risk for PEP by referring to the guidelines of both the American and European societies of gastrointestinal endoscopy.[3,4] However, there are no established eligibility criteria for high-risk patients. This makes it difficult to evaluate outcomes in high-risk patients without bias. Our study group also included both average-risk and high-risk patients. This heterogeneity may underestimate the benefit of pancreatic stenting, which is usually recommended for high-risk patients. Further study is therefore required to compare PEP prophylaxis directly between nonsteroidal anti-inflammatory drugs and combined pancreatic stenting in high-risk patients with established eligibility criteria.

The authors declare no conflict of interest.

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Immune Enhancement in Patients With Predicted Severe Acute Necrotizing Pancreatitis *Important Implications for Timing and Early Stratification*

To the Editor:

The report by Ke et al[1] of the randomized, double-blind, placebo-controlled, multicenter TRACE trial of early immune-enhancing thymosin alpha 1 (Tα1) in predicted severe acute necrotizing pancreatitis is of great interest, especially because there is no internationally agreed, specific, targeted therapy for acute pancreatitis. Unfortunately, unlike in severe sepsis[2] and chronic type B and C hepatitis, the TRACE trial did not find that Tα1 reduced the incidence of infected pancreatic necrosis (IPN), new-onset organ failure, or other complications of acute pancreatitis.

In acute pancreatitis, toxic insults induce acinar and ductal cell injury and death, promoting release of damage-associated molecular patterns, eg, mitochondrial deoxyribonucleic acid, high mobility group box-1 protein, and extracellular histones, which attract immune cells to the injured site.[3] Infiltrating monocytes/macrophages, neutrophils, and dendritic cells release inflammatory mediators and neuropeptides, exacerbating local and distant injury, and inducing cell death and organ dysfunction.[4] Crosstalk between cell death and organ dysfunction via inflammatory cascades feeds auto-amplification loops that exceed the critical threshold for persistent (<48 hours) organ failure that may lead to mortality.[5] Thus far, randomized trials of drugs targeted at a variety of pathogenetic mechanisms in acute pancreatitis have been disappointing,[6] at least in part attributable to late timing, problematic stratification, and choice of outcome measures (Table 1).

The Dutch Pancreatitis Study Group[7] and we[8] have recently confirmed that persistent organ failure and mortality have an early single peak, suggesting early intervention is required to halt disease progression. The TRACE trial recruited patients within 7 days of symptom onset with an Acute Physiology and Chronic Health Evaluation II (APACHE II) score ≥8 and Computerized Tomography Severity Index (CTSI) ≥5.[1] This resulted in the initiation of trial treatment at a mean of just over 4 days (96 hours) in intensive care unit settings, somewhat late for Tα1-based immunomodulatory therapy. $CD14^{hi}CD16^{-}$ monocyte human leucocyte antigen-DR (mHLA-DR) levels and T cell responses (especially $CD4^{+}$ T cells) are already reduced within 48 hours of disease onset, more so in those who are with persistent organ failure[9,10]; both mHLA-DR and $CD4^{+}$ T cell levels recover during clinical improvement. The TRACE trial did not select participants or tailor the Tα1 dose by measuring mHLA-DR, frequently used to assess immunosuppression in sepsis. The combination of APACHE II score ≥8 and CTSI ≥5 yielded only 192 of 508 patients (38%) with acute necrotizing pancreatitis. This unsatisfactory enrolment for a trial with IPN as the primary outcome measure may have diluted any effect of Tα1 because there was a trend toward

TABLE 1. Randomized, Double-Blind, Placebo-Controlled Drug Trials for Early Management of Acute Pancreatitis*

Trial Identifier	Year of Publication	Country	Centre, Blinding (Study Period)	Targeted AP Population (Admission)	Power Calculation	Time to Recruitment†	Trial Medication Starting Time‡	Patients Screened (Enrolled)	Drug Intervention	Primary Outcome Measure	Outcome
Clinical Trial Registry-India (CTRI/2010/091/001096)	2013	India	Multicenter (12 mo)	Elevated serum CRP level	No	NR	NR	NR (135)	Ulinastatin (200,000 IU, iv, bid, for 3 to 5 d)	Serum CRP level on day 7 vs baseline	NS
Clinical Trial Registry-India (CTRI/2009/000945)	2014	India	Single (36 mo)	Organ failure (OAC), APACHE II ≥8, or CTSI >7	No	<7 d	NR	282 (80)	Glutamine supplementation (20 g/d, po, bid, for 7 d)	Intestinal permeability§	NS
ClinicalTrials.gov Registry (NCT01292005)	2015	United States	Single (40 mo)	BMI >30 kg/m^2, APACHE II ≥8, hematocrit >45%, SIRS ≥2, abnormal chest radiograph, CT Balthazar grade D, E, or necrosis >30%	Yes	<72 h	Immediately	717 (28)	Pentoxifylline (400 mg, po, tid, for up to 3 d)	No. patients with LOHS >4 d	Improved‖
ClinicalTrials.gov Registry (NCT02897206)	2019	Croatia	Single (27 mo)	APACHE II ≥8	Yes	<72 h	NR	312 (101)	Imipenem-cilastatin (500 mg, iv, tid, for ideally 10 d [7–21 d])	Any infection (IPN, sepsis pneumonia, or any other infection)	NS
ClinicalTrials.gov Registry (NCT02487225)	2020	United States	Single (22 mo)	Any patients (RAC)	Yes	<72 h	Immediately	233 (84)	Pentoxifylline (400 mg, po, tid, for at least 3 d)	Composite outcome (SIRS, persistent organ failure, necrosis, IPN, need for ICU or intervention, death, or LOHS >4 d)	NS
ClinicalTrials.gov Registry (NCT01745861)	2020	UK	Single (21 mo)	Severe AP (OAC) or Glasgow (Imrie) score ≥3	Yes	<72 h	Immediately	198 (45)	Lipid emulsion enriched with omega-3 fatty acids (2 g/kg/d, iv, 14 h/d, for a maximum of 7 d or until discharge if sooner)	Serum CRP level on day 7 vs baseline	Improved
ClinicalTrials.gov Registry (NCT02692391)¶	2021	United States	Single (72 mo)	SIRS without organ failure	Yes	<72 h	NR	418 (42)	Indomethacin (100 mg, loading dose, no interval, rectally administered for the first time and 50 mg, maintenance doses, at 8-h intervals, rectally administered for 5 times)	The change in the SIRS score from randomization to 48 h vs baseline	NS
ClinicalTrials.gov Registry (NCT02473406)	2022	China	Multicenter (43 mo)	APACHE II ≥8, CTSI ≥5	Yes	<1 wk	NR	3569 (508)	Tα1 (1.6 mg, sc, bid, or at 12-h interval, for the first 7 d +1.6 mg, qd, or at 24-h interval, for the following 7 d)	Incidence of IPN at 90 d	NS

AP indicates acute pancreatitis; bid, bis in die; BMI, body mass index; CRP, C-reactive protein; ICU, intensive care unit; IPN, infectious pancreatic necrosis; iv, intravenous; LOHS, length of hospital stay; NR, not reported; NS, not significant; OAC, Original Atlanta Classification; po, per os; qd, quaque die; RAC, Revised Atlanta Classification; sc, subcutaneous; SIRS, systemic inflammatory response syndrome; tid, ter in die.

*PubMed was searched from January 1, 2013 (after RAC criteria published), to July 16, 2022, for relevant articles. The detailed search strategy was "Randomized controlled trial and 'acute pancreatitis'," and article type was randomized control trial. Records identified were 189 with 9 randomized, double-blind, placebo-controlled drug trials. One trial was excluded because it was mainly focusing on recovery from pancreatic exocrine insufficiency of AP patients.

†Time from initial symptoms onset to hospital admission or AP diagnosis.

‡Time from randomization to first trial medication administration.

§Assessed by urinary excretion of lactulose and mannitol and/or endotoxin levels (IgG and IgM).

‖This was later proved to be insignificant in a trial (NCT02692391) with larger sample size conducted by the same group.

¶Quadruple blind.

reduced IPN at 90 days. The wide 95% confidence intervals for IPN may be explained by the heterogeneous recruitment times, as well as the problematic patient selection and stratification for IPN as the primary outcome.

Clinical trials of new treatments are crucial to define a specific, targeted therapy for acute pancreatitis. The TRACE trial group is to be congratulated for its endeavors within the Chinese Acute Pancreatitis Clinical Trials Group. We hope there is TRACE 2 that addresses mHLA-DR–guided enrolment, stratification appropriate to outcome, and earlier Tα1 administration.

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Pancreatic Gangliocytic Paraganglioma: A Rare Neuroendocrine Neoplasm
Case Report and Literature Review

To the Editor:

First reported in 1957, gangliocytic paraganglioma (GP) is a morphologically distinct neuroendocrine tumor (NET) referred to as nonchromaffin paraganglioma or ganglioneuroma. Gangliocytic paragangliomas typically present as single tumors; however, in the setting of certain hereditary syndromes such as von Recklinghausen disease (neurofibromatosis 1), GPs may be multifocal.[1] Although GPs most commonly present in the second portion of the duodenum near the ampulla of Vater, they can occur in other sites within the gastrointestinal tract such as the esophagus, pylorus, and jejunum. Reported extragastrointestinal GPs have included the nasopharynx, thymus, lung, and ovary. Gangliocytic paraganglioma arising within the pancreas is an extremely rare phenomenon, with only 5 cases reported to date.[2–6] Herein, we describe our case and management of a pancreatic GP.

Gangliocytic paragangliomas are well-circumscribed tumors with a generally favorable prognosis, and literature documents very few reports of lymph node or systemic metastases.[3–5] Pathologically, GPs demonstrate a characteristic triphasic morphology in histopathology with epithelioid cells, spindle cells, and ganglionlike cells. Because these tumors are very rarely observed in the pancreas, they are challenging to differentiate from other pancreatic NETs.[7,8] Complete excision and accurate pathologic diagnosis are paramount for curative resection, and postoperative surveillance is strongly recommended.

Herein, we report an exceedingly rare case of a GP in the body of the pancreas and review the clinical presentation, differential diagnosis, surgical treatment, and histopathological features of this unique NET.

CLINICAL HISTORY

A 42-year-old man was referred to the surgical oncology service after evaluation of abdominal pain revealed a pancreatic body tumor on contrast-enhanced computed tomography scan of the abdomen and pelvis. The patient had no significant medical history or any personal or family history of inherited disorders or cancers. The patient was an active smoker with a history of social alcohol use. Physical examination found no abnormalities. Significant laboratory values included mild serum hyperglycemia of 178 mg/dL and an elevated serum amylase level of 1262 U/L. Biochemical tests including serum tumor markers were within reference limits.

Triple-phase contrast-enhanced cross-sectional imaging demonstrated a 1.5-cm hypodense, circumscribed lesion within the body of the pancreas (Fig. 1A). The surrounding pancreatic parenchyma and duct caliber was unremarkable, and there was no associated lymphadenopathy or vascular involvement. Staging computed tomography imaging of the chest found no concerning pathology. Endoscopic ultrasound evaluation and fine needle biopsy were performed; pathology was reported as neuroendocrine neoplasm. Immunohistochemistry found tumor cells positive for synaptophysin and chromogranin and negative for CD10, cyclin-D1, and CD117. Cytokeratin AE1/AE3 and CAM5.2 were weakly positive. Ki-67 was <2%. Gallium dotatate positron emission tomography imaging found no further evidence of disease.