ORIGINAL

Immune enhancement in patients with predicted severe acute necrotising pancreatitis: a multicentre double-blind randomised controlled trial

Lu Ke[1,25], Jing Zhou[1,2], Wenjian Mao[2], Tao Chen[3], Yin Zhu[4], Xinting Pan[5], Hong Mei[6], Vikesh Singh[7], James Buxbaum[8], Gordon Doig[9], Chengjian He[10], Weili Gu[11], Weihua Lu[12], Shumin Tu[13], Haibin Ni[14], Guoxiu Zhang[15], Xiangyang Zhao[16], Junli Sun[17], Weiwei Chen[18], Jingchun Song[19], Min Shao[20], Jianfeng Tu[21], Liang Xia[4], Wenhua He[4], Qingyun Zhu[5], Kang Li[6], Hongyi Yao[10], Jingyi Wu[12], Long Fu[13], Wendi Jiang[1], He Zhang[22], Jiajia Lin[1], Baiqiang Li[1], Zhihui Tong[1*], John Windsor[23], Yuxiu Liu[1,24] and Weiqin Li[1,2,25*] on behalf of the Chinese Acute Pancreatitis Clinical Trials Group (CAPCTG)

© 2022 Springer-Verlag GmbH Germany, part of Springer Nature

Abstract

Purpose: Infected pancreatic necrosis (IPN) is a highly morbid complication of acute necrotising pancreatitis (ANP). Since there is evidence of early-onset immunosuppression in acute pancreatitis, immune enhancement may be a therapeutic option. This trial aimed to evaluate whether early immune-enhancing Thymosin alpha 1 (Tα1) treatment reduces the incidence of IPN in patients with predicted severe ANP.

Methods: We conducted a multicentre, double-blind, randomised, placebo-controlled trial involving ANP patients with an Acute Physiology and Chronic Health Evaluation II (APACHE II) score ≥ 8 and a computed tomography (CT) severity score ≥ 5 admitted within 7 days of the advent of symptoms. Enrolled patients were assigned to receive a subcutaneous injection of Tα1 1.6 mg every 12 h for the first 7 days and 1.6 mg once a day for the subsequent 7 days or matching placebos (normal saline). The primary outcome was the development of IPN during the index admission.

Results: A total of 508 patients were randomised, of whom 254 were assigned to receive Tα1 and 254 placebo. The vast majority of the participants required admission to the intensive care unit (ICU) (479/508, 94.3%). During the index admission, 40/254(15.7%) patients in the Tα1 group developed IPN compared with 46/254 patients (18.1%) in the placebo group (difference -2.4% [95% CI − 7.4 to 5.1%]; $p = 0.48$). The results were similar across four predefined subgroups. There was no difference in other major complications, including new-onset organ failure (10.6% vs. 15%), bleeding (6.3% vs. 3.5%), and gastrointestinal fistula (2% vs. 2.4%).

*Correspondence: njzyantol@aliyun.com; ctgchina@medbit.cn
[1] Department of Critical Care Medicine, Jinling Hospital, Medical School of Nanjing University, No. 305 Zhongshan East Road, Nanjing 210000, Jiangsu, China
Full author information is available at the end of the article

Springer

Conclusion: The immune-enhancing Tα1 treatment of patients with predicted severe ANP did not reduce the incidence of IPN during the index admission.

Keywords: Acute pancreatitis, Immunosuppression, Thymosin, Pancreatic necrosis, Infection

Introduction

The annual global incidence of acute pancreatitis (AP) is estimated to be 34 per 100,000 individuals [1]. A smaller subgroup of patients with AP (5–10%) develop acute necrotising pancreatitis (ANP) [2] and can experience a more prolonged disease course that commonly requires intensive care unit (ICU) admission, especially if infected pancreatic necrosis (IPN) develops [3, 4]. The bacteria responsible for IPN are often translocated from the gastrointestinal tract and reach the pancreas through several different transmission routes, including haematogenous, lymphatic, and transcoelomic [5, 6].

Attempts to reduce the risk of infection in ANP have included the use of prophylactic antibiotics [7] and enteral probiotics [8]. The former is no longer recommended because of issues like antibiotic resistance, methodological quality in previous studies, and fungal superinfection [9, 10]. The latter is controversial, as a prominent randomised controlled trial found an increased risk of gastrointestinal necrosis associated with probiotic treatment [8]. Given that there is evidence of immunosuppression in the early phase of AP and it is associated with infectious complications [11–14], a theoretical strategy to reduce the risk of IPN is to boost the host defence (immune enhancement) against bacterial infection [15].

Thymosin alpha 1 (Tα1), a polypeptide hormone isolated from the thymus, stimulates both innate and adaptive immunity [16]. In a pilot study of patients with AP, Tα1 was effective in reducing the risk of developing IPN [17]. Based on this preliminary data, we conducted a multicentre randomised clinical trial to determine the effect of Tα1 treatment. We hypothesised that early immune enhancement with Tα1 may reduce the incidence of IPN in predicted severe ANP. The main results of this trial were presented at American Pancreatic Association (APA) 2021 Annual Meeting and published as an abstract [18].

Methods

Trial design and oversight

This is a multicentre, double-blind, randomised, placebo-controlled, parallel-group trial to assess the efficacy of Tα1 in addition to standard care on the development of IPN in patients with predicted severe ANP. The trial was approved by the local hospital ethics committees of all the participating sites and registered on the

Take-home message

Compared with placebo, immune-enhancing Thymosin α1 treatment did not reduce the incidence of infected pancreatic necrosis in patients with predicted severe acute necrotising pancreatitis. However, it might be effective in specific subgroups of acute necrotising pancreatitis, like patients with extended pancreatic necrosis.

ClinicalTrials.gov Registry (NCT02473406) before enrolment commenced. The trial protocol was published in 2020 [19], and the full protocol and statistical analysis plan are available in the Supplementary Protocol. This study was funded by the Science and Technology Project of Jiangsu Province of China (no. SBE2016750187) and partly supported by SciClone Pharmaceuticals Holding Limited, which provided trial drugs and support for meetings during the study period. The funders were not involved in the trial's design, data collection, interpretation, or manuscript preparation.

Study population

Patients diagnosed with AP aged 18 to 70 years and with an Acute Physiology and Chronic Health Evaluation II (APACHE II) score ≥ 8 and computed tomography (CT) severity score [20] ≥ 5 admitted to any of the participating sites within seven days of the onset of abdominal pain were eligible for inclusion. The diagnosis of AP was based on the Revised Atlanta Classification (RAC) criteria [2]. Patients were excluded if they were pregnant, had a history of chronic pancreatitis, had underlying malignancy, received intervention for pancreatic necrosis prior to enrolment, had a known history of severe cardiovascular, respiratory, renal, or hepatic diseases, or had pre-existing immune disorders such as acquired immune deficiency syndrome (AIDS). Detailed inclusion and exclusion criteria are provided in the Supplementary Protocol.

At each site, informed consent was obtained from the patients or their next of kin before randomisation. Patients were enrolled from March 18, 2017, to December 10, 2020. Follow-up was completed on March 10, 2021.

Randomisation, masking and interventions

Each eligible participant was assigned randomly from a computer-generated sequence to either the Tα1 or placebo group in a 1:1 ratio, using a block size of 4 stratified by site. The random allocation sequence was generated

by an independent statistician at the Jinling Hospital. Allocation concealment was achieved using blinded medication packs. Patients were assigned to receive a subcutaneous injection of Tα1 (SciClone Pharmaceutical Co., Ltd, Hong Kong) 1.6 mg every 12 h for the first 7 days and 1.6 mg once a day for the following 7 days or a matching placebo (normal saline, Chengdu Tongde Pharmaceutical Co., Ltd, Chengdu) during the same period. The trial drug was administered for a maximum of 14 days, or until hospital discharge or death, whichever occurred first.

Participants, treating physicians, and investigators were blinded to the treatment allocation to minimise potential bias. The trial statistician was also blinded when developing the statistical programmes. Tα1 and placebo were supplied in identically labelled individual vials. All other aspects of the patients' care were provided based on the international guidelines [21]. Prophylactic antibiotics were not recommended accordingly. For the management of IPN, intervention was indicated when the collection was suspected or confirmed to be infected, and preferably after four weeks from the onset of the disease, per the guidelines [21]. Technically, either a surgical or endoscopic step-up approach was applied based on the location and morphology of the collection and the technical expertise available at each participating site. The decision for a fine-needle aspiration or invasive therapeutic intervention was made by the senior treating clinician. The details for the management of AP are described in the published protocol [19] and in the Supplementary Protocol.

Data collection
A web-based database (Unimed Scientific Inc., Wuxi, China) was developed for data collection (accessed at capctg.medbit.cn). Before enrolment, a start-up meeting for data entry and storage training was organised at each participating site to ensure high-quality data collection.

Trial outcomes
The primary outcome was the development of IPN during the index admission. We define the term "index admission" as the first admission in a series of hospital admissions. The diagnosis of IPN was made when one or more of the following criteria were present: gas bubbles within pancreatic and/or peripancreatic necrosis on CT; a positive culture from pancreatic and/or peripancreatic necrosis obtained by fine-needle aspiration, drainage, or necrosectomy [2]. All the reported positive cases were reviewed by a remote adjudication committee. Decisions of the remote adjudicating committee

took precedence over the treating clinicians. Secondary clinical outcomes include IPN at 90 days after randomisation and new-onset organ failure as defined by the Revised Atlanta Classification [2], mortality, bleeding requiring intervention, gastrointestinal fistula requiring intervention, positive blood culture, and pancreatic fistula during the index admission. Secondary laboratory outcomes include C-reactive protein (CRP), monocyte human leukocyte antigen-DR (mHLA-DR), and lymphocyte count on day 7 and day 14 after randomisation and positive blood cultures. The details and definitions of all outcomes are provided in the Supplementary Protocol.

Statistical analysis
The incidence of IPN during the index admission in our study population was approximately 25%, according to our previous studies [22, 23]. A sample size of 520 patients was estimated to provide 80% power at a 2-sided alpha of 5% to demonstrate an absolute risk reduction of 10% in IPN during the index admission (25% in the placebo group vs 15% in the Tα1 group) after accounting for 4% dropouts (PASS V.11, NCSS software, Kaysville, USA). The treatment effect was estimated based on our pilot study, which demonstrated an 80% relative reduction in the incidence of IPN (42 to 8%) [17].

Primary analyses were based on the intention-to-treat (ITT) population, and secondary sensitivity analyses were done on the per-protocol (PP) population for the primary outcome and key secondary outcomes. Continuous data are reported as means and standard deviations or as medians and interquartile ranges as appropriate, depending on their normality. Categorical data are expressed as numbers and percentages.

The generalised linear model (GLM) was employed to compare group differences and calculate the risk difference for the primary outcome, together with its 95% confidence intervals. The GLM was also employed to analyse secondary outcomes with treatment as the predictor. Kaplan–Meier curves were used to compare the cumulative incidence of IPN to 90 days after randomisation tested by log-rank test. Detailed descriptions for the analyses could be found in the Supplementary statistical analysis plan. Four subgroups were predefined for the evaluation of the incidence of IPN during the index admission and 90 days after randomisation: the severity of AP (severe and non-severe [2]), age (>60 and ≤60 years old), etiologies of AP (biliary and non-biliary) and extent of pancreatic necrosis (>50% and ≤50%).

Analyses were conducted using SAS 9.4®. Statistical tests will be two sided, and p values < 0.05 will be deemed

as significant. All authors had access to the study data and had reviewed and approved the final manuscript.

Results

Results of recruitment and baseline characteristics

During the study period, 3569 AP patients were assessed for eligibility, of whom 508 were enrolled in the trial at 16 hospitals across China. The numbers of cases from each site are shown in online supplemental Table S1. Among those 508 randomised patients, 254 were assigned to receive Tα1 and 254 placebo. The most common reasons for exclusion were admission > 7 days before evaluation and APACHE score < 8. Ten patients (2%) received the study drug on the randomisation day, while the others did so on the following day. Eleven patients in the Tα1 group and eight patients in the placebo group withdrew consent during treatment but did not refuse follow-up and data usage (Fig. 1). Three patients in the placebo group stopped research intervention midway due to adverse reactions.

Baseline demographics and characteristics were not significantly different between the Tα1 and placebo groups (Table 1). Hypertriglyceridemia was the leading cause of AP in both groups, accounting for approximately half of the cases (48.8% vs. 50%). The vast majority of the trial participants required ICU admission(479/508, 94.3%). The numbers of patients who received the trial agent on each trial day are shown in online supplemental Table S2.

Primary outcome and secondary outcomes

During the index admission, 40/254 (15.7%) patients in the Tα1 group developed IPN compared with 46/254 patients (18.1%) patients in the placebo group (difference −2.4% [95% CI −7.4 to 5.1%]; $p = 0.48$). Of the 86 IPN patients, 74 were diagnosed according to microbiological results(66 obtained during catheter drainage procedures, 8 during open surgery), and 12 were based on radiological findings alone. No fine-needle aspiration procedure was performed during the TRACE trial. At 90 days after randomisation, 57/254 (22.4%) patients in the Tα1 group developed IPN compared with 65/254 patients (25.6%) in the placebo group (difference −3.3% [95% CI −9.2 to 4.8%]; $p = 0.39$). For the 74 microbiologically confirmed IPN patients, the microorganisms we found are shown in online supplemental Table S3. There was no difference in mortality between groups either within the index admission or at 90 days after randomisation (Table 2). The Kaplan–Meier curves for the cumulative incidence of IPN until 90 days after randomisation are shown in Fig. 2. There was no significant difference in the probability of developing IPN between the Tα1 and placebo groups (Log-Rank $p = 0.39$). The results of the per-protocol analysis of the primary outcome and key secondary outcomes are shown in online supplemental Table S4.

There was no difference in other major complications, including new-onset organ failure (10.6% vs. 15%; difference −4.3% [95% CI −8.2 to 1.9%]; $p = 0.15$), bleeding (6.3% vs. 3.5%; difference 2.8 [95% CI −0.7 to 10.5]; $p = 0.15$), and gastrointestinal fistula (2% vs. 2.4%; difference −0.4% [95% CI −1.8 to 3.9%]; $p = 0.75$) during the index admission. Moreover, there were no significant differences in length of ICU or hospital stay, the requirement for catheter drainage, minimally invasive debridement, or open surgery (Table 2). For mHLA-DR, no difference was detected on day7 and day14 between groups (online supplemental Table S5). The additional secondary endpoints regarding organ failure and laboratory parameters are shown in online supplemental Tables S5–6.

Subgroup analyses

There was no significant heterogeneity in the effect of Tα1 on the incidence of IPN during the index admission and 90 days after randomisation in any of the four predefined subgroups (Fig. 3, online supplemental Tables S7–8). In a post hoc subgroup analysis, the effect of Tα1 did not differ in patients caused by hypertriglyceridemia or other etiologies (online supplemental Tables S7–8).
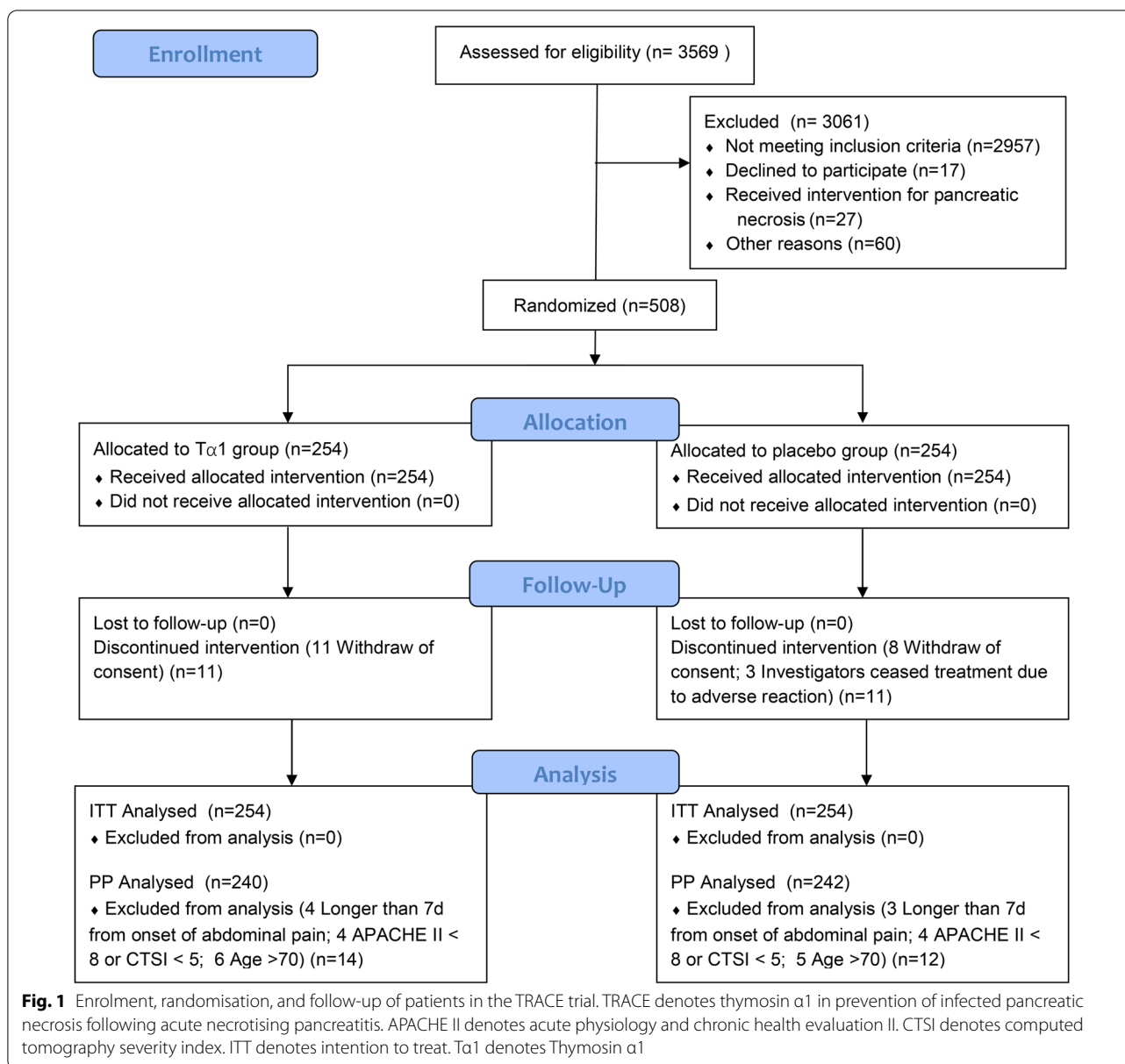
Adverse events

Adverse events occurred in 21 patients in the Tα1 group and 19 in the placebo group (8.3% vs. 7.5%, $p = 0.742$) (online supplemental Table S9). The most common adverse event was venous thrombosis which occurred in 6 patients (2.4%) in the Tα1 group vs. 5 (2%) in the placebo group. All adverse events are listed in online supplemental Table S9.

Discussion

In this multicentre, double-blind, randomised, placebo-controlled trial, immune enhancement using Tα1 did not significantly reduce the incidence of IPN during the index admission or within 90 days of randomisation in patients with ANP. Given the varied range of severity of AP [2], this study was designed to select more severe patients based on the APACHE II score at enrolment [24]. However, we failed to show a difference in the primary outcome.

Our results are not consistent with the results from an experimental animal study [17] and the pilot clinical study [25]. There are several possible explanations. First, current animal models cannot recapitulate all aspects of human AP, especially for a complication like IPN, which often occurs several weeks after admission [26,

Fig. 1 Enrolment, randomisation, and follow-up of patients in the TRACE trial. TRACE denotes thymosin α1 in prevention of infected pancreatic necrosis following acute necrotising pancreatitis. APACHE II denotes acute physiology and chronic health evaluation II. CTSI denotes computed tomography severity index. ITT denotes intention to treat. Tα1 denotes Thymosin α1

27]. Second, the pilot study recruited only 24 patients from a single centre, making its findings vulnerable to type I error. Third, the dose regimen in this trial is different from the pilot one with a longer duration of drug administration (one week in the pilot vs. two weeks in the present) and a lower initial dose (6.4 mg per day in the pilot vs. 3.2 mg per day in the present). There were two time-course considerations in designing the dose regimen: (1) infection mainly occurs beyond the second week after disease onset [3, 28], and a 2-week regimen should be able to cover the period interval better when prevention is possible; (2) immunosuppression typically develops early in the first week and usually slowly

recovers during the second week [12], which is the reason for prescribing half the dose during the second week of treatment. A similar step-wise dose reduction was used in a previous study testing Tα1 in sepsis [29], showing that Tα1 could reduce 28-day mortality. Moreover, since Tα1 has a short elimination half-life ranging from 1.7 to 2.1 h [30], an expanded drug administration period may exert better effects. Besides, the incidence of IPN during the index admission is lower than expected in the placebo group (18.1% vs. 25% for sample size estimation), which might make our trial underpowered. Before initiation of recruitment, we changed the time interval of the primary outcome from "28 days" to time until "index hospital

Table 1 Baseline characteristics of the study subjects

Characteristics	Tα1 group (N=254)	Placebo group (N=254)
Age, mean (SD), y	44.3 (13.2)	45.4 (13.4)
Gender		
Women, (n, %)	92 (36.2)	97 (38.2)
Men, (n, %)	162 (63.8)	157 (61.8)
BMI, mean (SD), kg/m^2	26.4 (3.9)	26.8 (4.2)
Etiologies		
Alcoholic, (n, %)	17 (6.7)	15 (5.9)
Biliary, (n, %)	101 (39.8)	100 (39.4)
Idiopathic, (n, %)	12 (4.7)	12 (4.7)
Hypertriglyceridemia, (n, %)	124 (48.8)	127 (50)
Charlson score, mean (SD)	0.6 (0.7)	0.5 (0.8)
Interval between onset and hospital admission, mean (SD),d	2.9 (2.5)	3.0 (1.9)
Interval between onset and ICU admission, mean (SD),d	3.2 (2.7)	3.2 (1.9)
Interval between onset and randomisation, mean (SD),d	4.2 (2.6)	4.1 (2)
Extent of pancreatic necrosis		
<30%, (n, %)	165 (65)	151 (59.4)
30–50%, (n, %)	55 (21.7)	72 (28.3)
>50%, (n, %)	34 (13.4)	31 (12.2)
Disease severity		
CTSI score, median (IQR)	6 (5–8)	6 (5–8)
APACHE II score, median (IQR)	10 (8–13)	10 (8–13)
BISAP score, median (IQR)	2 (1–2)	2 (1–2)
PASS score, median (IQR)	235 (190–523)	235 (190–550)
CRP, median (IQR), mg/L	172.1 (95.4–236.2)	160.6 (105.5–236.4)
Lymphocyte count, median (IQR), ×10^9/L	0.9 (0.6–1.2)	0.9 (0.7–1.2)
SOFA score, median (IQR)	4 (2–6)	4 (2–6)
Respiration, median (IQR)	2 (1–2)	2 (1–2)
Cardiovascular, median (IQR)	0 (0–0)	0 (0–0)
Renal, mean median (IQR)	0 (0–1)	0 (0–1)
Requirement of organ support at randomisation		
Mechanical ventilation, (n, %)	63 (24.8)	69 (27.2)
Renal replacement therapy, (n, %)	63 (24.8)	63 (24.8)
Vasoactive agents, (n, %)	30 (11.8)	26 (10.2)

$p > 0.05$ for the comparison between the groups for all characteristics. SD denotes standard deviation. BMI denotes body mass index. ICU denotes intensive care unit. IQR denotes interquartile range. CTSI denotes computed tomography severity index. APACHE II denotes acute physiology and chronic health evaluation II, which ranges from 0 to 71, with higher scores indicating more severe disease. BISAP denotes bedside index for severity in acute pancreatitis. PASS denotes pancreatitis activity scoring system. CRP denotes C-reactive protein. SOFA denotes sequential organ failure assessment, which ranges from 0 to 24, with higher scores indicating more severe organ failure. Tα1 denotes thymosin α1

discharge" due to concerns regarding loss of follow-ups and the possibility of incomplete data. During the trial, we followed up with all the participants for 90 days after randomisation, and the incidence of IPN was 25.6% in the placebo group by then. Still, the Tα1 treatment did not result in a reduction of IPN by 90 days after randomisation. Last, since we chose either microbiologically or radiologically confirmed IPN as our primary outcome, underestimating the number of infections is highly likely. Patients with IPN that resolved without invasive intervention and did not present with CT evidence of air within the collection were not diagnosed as IPN in the TRACE trial. Moreover, fine-needle aspiration was not used in the TRACE trial, since the guidelines do not recommend this procedure considering substantial false-negative results [21, 31]. However, this may also contribute to an underestimation of IPN patients.

There is evidence to support a shifting balance between the systemic pro-inflammatory response and the compensatory anti-inflammatory response over the early
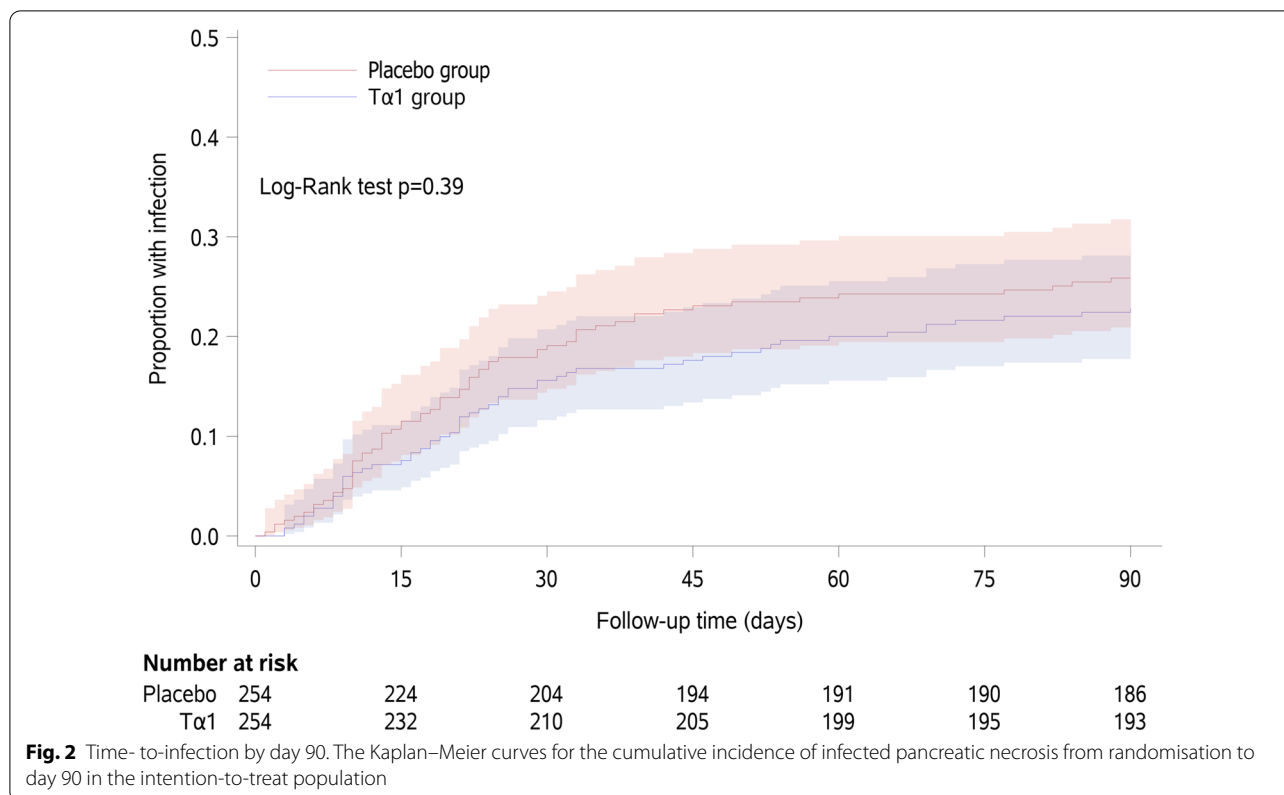
Table 2 Primary and secondary endpoints

	Tα1 group (N = 254)	Placebo group (N = 254)	Risk difference (95% CI)	p value
Primary endpoint				
IPN during the index admission, (n, %)	40 (15.7)	46 (18.1)	− 2.36 (− 7.41, 5.07)	0.48
Secondary endpoints*				
New-onset organ failure	27 (10.6)	38 (15)	− 4.26 (− 8.18, 1.93)	0.15
Respiratory, (n, %)	9 (3.5)	17 (6.7)	− 3.15 (− 5.08, 1.08)	0.11
Renal, (n, %)	10 (3.9)	7 (2.8)	1.25 (− 1.19, 7.48)	0.43
Cardiovascular, (n, %)	14 (5.5)	20 (7.9)	− 2.33 (− 5.00, 2.82)	0.30
Mortality (n, %)	18 (7.1)	22 (8.7)	− 1.55 (− 4.73, 4.21)	0.52
90-Day mortality (n, %)	23 (9.1)	23 (9.1)	0.03 (− 3.79, 6.63)	0.99
IPN within 90 days after randomisation (n, %)	57 (22.4)	65 (25.6)	− 3.25 (− 9.18, 4.83)	0.39
Bleeding, (n, %)	16 (6.3)	9 (3.5)	2.80 (− 0.69, 10.53)	0.15
Positive blood culture (n, %)	18 (7.1)	25 (9.8)	− 2.73 (− 5.85, 2.83)	0.27
Gastrointestinal fistula, (n, %)	5 (2)	6 (2.4)	− 0.41 (− 1.76, 3.91)	0.75
Length of ICU stay, mean (SD), d	14.4 (16.2)	13.6 (16.4)	0.75 (− 2.07, 3.57)	0.60
Length of hospital stay, mean (SD), d	21.0 (21.3)	20.5 (20)	0.46 (− 3.12, 4.03)	0.80
In-hospital cost, mean (SD), Kyuan	143 (177)	138 (206)	5 (− 28, 38)	0.77
Use of invasive interventions				
Requiring catheter drainage (n, %)[#]	36 (14.2)	39 (15.4)	− 1.27 (− 6.08, 6.02)	0.69
Requiring MI debridement (n, %)[**]	17 (6.7)	12 (4.7)	1.96 (− 1.44, 8.91)	0.34
Requiring open surgery (n, %)	8 (3.1)	5 (2)	1.14 (− 0.93, 7.37)	0.41
Number of procedures in patients requiring invasive interventions during the index admission				
Number of catheter drainage procedures, median (IQR)[+]	2.5 (1–4)	2 (1–3)	0.14 (− 0.58, 0.85)	0.71
Number of MI debridement procedures, median (IQR)[++]	3 (2–6)	4 (3–5)	− 0.52 (− 1.95, 0.91)	0.48

CI denotes confidential interval. IPN denotes infected pancreatic necrosis. ICU denotes intensive care unit. MI denotes minimally invasive. *All secondary endpoints were registered during the index admission unless otherwise specified; [#] both percutaneous and transluminal drainage included; **27 patients underwent exclusive percutaneous surgical MI debridement, one patient underwent exclusive endoscopic transluminal debridement, and one combined; [+] only patients undergoing catheter drainage procedures are included; [++] only patients undergoing MI debridement procedures are included

course of AP [13, 32]. It was considered that the pro-inflammatory response occurs in the first few days to weeks and that the compensatory anti-inflammatory response occurs later. However, analyses in patients with sepsis and AP suggest that these responses can also run in parallel and that there is an association between early-onset immunosuppression and poor outcomes in AP, including increased risk of infectious complications [33, 34]. In sepsis patients, immune-enhancing therapies had been evaluated with agents like Tα1 [29] and nivolumab [35]. In AP patients, previous trials investigating immunomodulatory therapy to block the early pro-inflammatory response have not been convincing[36], and this includes drugs like lexipafant [37, 38] and octreotide [39]. In patients with severe COVID-19, observational studies showed that Tα1 attenuated lung injury and decreased mortality [40, 41]. Despite the theoretical benefits of immune enhancement with Tα1 and the encouraging results from the pilot study [17], Tα1 did not reduce the incidence of IPN or improve any of the clinical outcomes in this trial.

In the subgroup analyses, larger treatment effects were seen in patients with a greater extent of pancreatic necrosis (> 50%) and those aged more than 60 years old, although not statistically significant. We should interpret all the subgroup results with caution. First, the power was not enough to detect the differences among treatments. Second, the definition of necrosis is relatively subject based on a single CT scan. Third, we excluded patients with advanced age because age ≥ 70 years is an independent risk factor for mortality in severe AP [42], and the immune system becomes slower and less responsive over age [43], thereby limiting the chance to observe

Fig. 2 Time- to-infection by day 90. The Kaplan–Meier curves for the cumulative incidence of infected pancreatic necrosis from randomisation to day 90 in the intention-to-treat population

the treatment effect. However, excluding these patients makes the study subgroup for elderly patients even smaller.

In line with the excellent safety profile reported in previous studies, Tα1 showed satisfactory safety performance in this trial. Three patients discontinued treatment due to adverse reactions (one erythema and two unexplainable fever) but received the placebo. For the other secondary outcomes, although the incidence of bleeding did not differ from previous reports [44] and was not significantly higher in the intervention group, we strongly recommend future studies regarding necrotising pancreatitis monitor this potentially lethal complication.

The study has several limitations. The first is that the incidence of IPN may have been affected by the use of antibiotics and the criterion for repeating a CT scan because they were not mandatory standardised but left to the clinical team to decide. The second is that there were problems (failed multisite lab standardisation) with the measurement of mHLA-DR, a validated cell-surface signature for risk stratification in critically ill patients [45]. We obtained mHLA-DR data from less than half

of the study subjects, which may be underpowered to detect the difference between groups. The third is that APACHE II misclassifies the severity of AP in almost a third of patients, which could also have contributed to the negative results [46]. Moreover, the timing of treatment might have been too late. The current trial included patients up to one week after the advent of symptoms, which may increase the heterogeneity of the study population. Apart from the timing, the appropriate duration of therapy is unclear. Last, nearly 50% of the study patients had hypertriglyceridemia as etiology, significantly higher than results from an international registry [47]. The increase of hypertriglyceridemia-induced AP in Chinese cohorts might be attributed to changes in dietary habits [48] and genetic factors [49]. Although the effect of Tα1 did not vary across patients caused by hypertriglyceridemia or other etiologies, the distinct etiological distribution leaves the generalisability of the observed results in doubt.

In conclusion, the immune-enhancing Tα1 treatment of patients with predicted severe ANP (APACHE II ≥ 8 at enrolment) did not significantly reduce the incidence
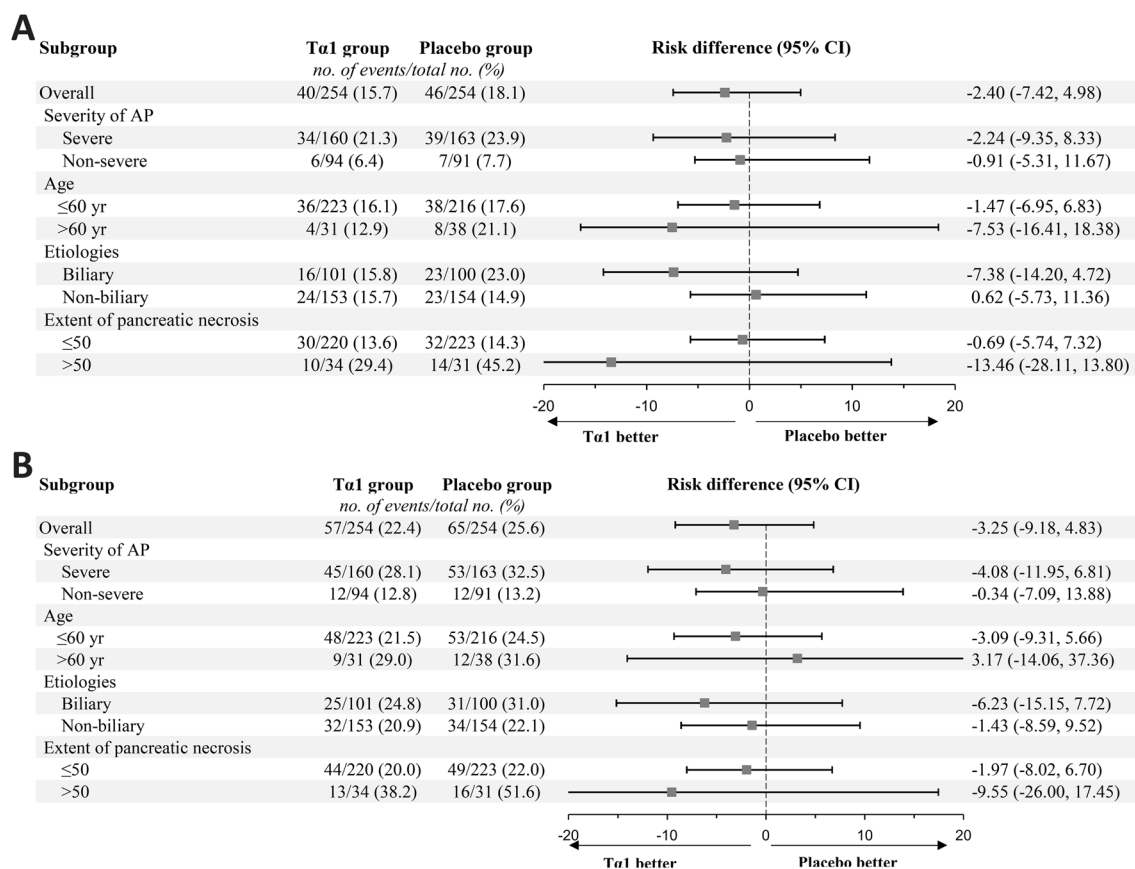
Fig. 3 Subgroup analysis of the risk of infected pancreatic necrosis by the index hospital discharge and day 90. Panel A shows the risk difference of infected pancreatic necrosis during the index admission between the two treatment groups. Panel B shows the risk difference of infected pancreatic necrosis up to 90 days after randomisation. A risk difference of less than 0 indicates better results for the Tα1 group

of IPN during the index admission compared with placebo. Future trials seeking to investigate this approach will need to determine the best way to select patients and decide on the most effective dose and duration of Tα1 treatment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06745-7.

Author details

[1] Department of Critical Care Medicine, Jinling Hospital, Medical School of Nanjing University, No. 305 Zhongshan East Road, Nanjing 210000, Jiangsu, China. [2] Department of Critical Care Medicine, Jinling Hospital, Nanjing Medical University, Nanjing 210010, Jiangsu, China. [3] Department of Public Health, Policy and Systems, Institute of Population Health, Whelan Building, Quadrangle, The University of Liverpool, Liverpool L69 3GB, UK. [4] Pancreatic Disease Centre, Department of Gastroenterology, The First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi, China. [5] Department of Emergency Intensive Care Unit, The Affiliated Hospital of Qingdao University, Qingdao 266000, Shandong, China. [6] Department of Critical Care Medicine, The Affiliated Hospital of Zunyi Medical University, Zunyi 536000, Guizhou, China. [7] Pancreatitis Centre, Division of Gastroenterology, Johns Hopkins Medical Institutions, Baltimore, MD, USA. [8] Division of Gastroenterology, Department of Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, USA. [9] Northern Clinical School, Royal, North Shore Hospital, University of Sydney, Sydney, Australia. [10] Department of Critical Care Medicine, the Affiliated Nanhua Hospital, University of South China, Hengyang 421002, Hunan, China. [11] Department of Critical Care Medicine, Affiliated Hospital 2 of Nantong University, Nantong 226000, Jiangsu, China. [12] Department of Intensive Care Unit, The First Affiliated Hospital of Wannan Medical College, Wuhu 241001, Anhui, China. [13] Department of Emergency Medicine, Shangqiu First People's Hospital, Shangqiu 476000, Henan, China. [14] Department of Emergency Medicine, Jiangsu Provincial Hospital of Integrated Chinese and Western Medicine, Nanjing 210010, Jiangsu, China. [15] Department of Emergency Medicine, The First Affiliated Hospital and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, Henan, China. [16] Department of Intensive Care Unit, Qilu Hospital of Shandong University, Qingdao 266000, Shandong, China. [17] Department of Intensive Care Unit, Luoyang Central Hospital, Zhengzhou University, Luoyang 471100, Henan, China. [18] Department of Gastroenterology, Clinical Medical College, Yangzhou University, Yangzhou, Jiangsu, China. [19] Department of Critical Care Medicine, 94Th Hospital of PLA, Nanchang 330006, Jiangxi, China. [20] Department of Intensive Care Unit, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, Anhui, China. [21] Department of Emergency Medicine, Zhejiang Provincial People's Hospital, Hangzhou 310014, Zhejiang, China. [22] Department of Critical Care Medicine, Jinling Hospital, Medical School of Southeast University, Nanjing 210002, Jiangsu, China. [23] Surgical and Translational Research Centre, Faculty of Medical and Health Sciences, University of Auckland, Auckland 1142, New Zealand. [24] Department of Medical Statistics, Jinling Hospital, Medical School of Nanjing University, Nanjing 210002, Jiangsu, China. [25] National Institute of Healthcare Data Science, Nanjing University, Nanjing 210010, Jiangsu, China.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in pub-lished maps and institutional affiliations.

References

1. Xiao AY, Tan ML, Wu LM, Asrani VM, Windsor JA, Yadav D, Petrov MS (2016) Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol 1:45–55
2. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS, Acute Pancreatitis Classification Working G (2013) Classification of acute pancreatitis–2012: revision of the Atlanta classifica-tion and definitions by international consensus. Gut 62:102–111
3. Trikudanathan G, Wolbrink DRJ, van Santvoort HC, Mallery S, Freeman M, Besselink MG (2019) Current concepts in severe acute and necrotiz-ing pancreatitis: an evidence-based approach. Gastroenterology 156(1994–2007):e1993
4. Schepers NJ, Bakker OJ, Besselink MG, Ahmed Ali U, Bollen TL, Gooszen HG, van Santvoort HC, Bruno MJ, Dutch Pancreatitis Study G (2019) Impact of characteristics of organ failure and infected necrosis on mortal-ity in necrotising pancreatitis. Gut 68:1044–1051
5. Mowbray NG, Ben-Ismaeil B, Hammoda M, Shingler G, Al-Sarireh B (2018) The microbiology of infected pancreatic necrosis. Hepatobiliary Pancreat Dis Int 17:456–460
6. Mittal A, Phillips AR, Middleditch M, Ruggiero K, Loveday B, Delahunt B, Cooper GJ, Windsor JA (2009) The proteome of mesenteric lymph during acute pancreatitis and implications for treatment. JOP 10:130–142
7. Wittau M, Mayer B, Scheele J, Henne-Bruns D, Dellinger EP, Isenmann R (2011) Systematic review and meta-analysis of antibiotic prophylaxis in severe acute pancreatitis. Scand J Gastroenterol 46:261–270
8. Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJ, Rosman C, Ploeg RJ, Brink MA, Schaapherder AF, Dejong CH, Wahab PJ, van Laarhoven CJ, van der Harst E, van Eijck CH, Cuesta MA, Akkermans LM, Gooszen HG (2008) Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet 371:651–659
9. Lim CL, Lee W, Liew YX, Tang SS, Chlebicki MP, Kwa AL (2015) Role of antibiotic prophylaxis in necrotizing pancreatitis: a meta-analysis. J Gas-trointest Surg 19:480–491
10. de Vries AC, Besselink MG, Buskens E, Ridwan BU, Schipper M, van Erpe-cum KJ, Gooszen HG (2007) Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis: relationship between methodo-logical quality and outcome. Pancreatology 7:531–538
11. Ueda T, Takeyama Y, Yasuda T, Shinzeki M, Sawa H, Nakajima T, Ajiki T, Fujino Y, Suzuki Y, Kuroda Y (2006) Immunosuppression in patients with severe acute pancreatitis. J Gastroenterol 41:779–784

12. Yu WK, Li WQ, Li N, Li JS (2004) Mononuclear histocompatibility leukocyte antigen-DR expression in the early phase of acute pancreatitis. Pancreatology 4:233–243

13. Pan T, Zhou T, Li L, Liu Z, Chen Y, Mao E, Li M, Qu H, Liu J (2017) Monocyte programmed death ligand-1 expression is an early marker for predicting infectious complications in acute pancreatitis. Crit Care 21:186

14. Li J, Yang WJ, Huang LM, Tang CW (2014) Immunomodulatory therapies for acute pancreatitis. World J Gastroenterol 20:16935–16947

15. Hotchkiss RS, Monneret G, Payen D (2013) Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy. Nat Rev Immunol 13:862–874

16. Garaci E (2007) Thymosin alpha1: a historical overview. Ann N Y Acad Sci 1112:14–20

17. Wang X, Li W, Niu C, Pan L, Li N, Li J (2011) Thymosin alpha 1 is associated with improved cellular immunity and reduced infection rate in severe acute pancreatitis patients in a double-blind randomized control study. Inflammation 34:198–202

18. (2021) Abstracts of Papers Submitted to the 52nd Meeting of the American Pancreatic Association, November 3–6, 2021, Miami Beach, Florida. Pancreas 50: 1044–1115

19. Zhou J, Mao W, Ke L, Chen T, He W, Pan X, Chen M, He C, Gu W, Wu J, Song J, Ni H, Tu J, Sun J, Zhang G, Chen W, Xue B, Zhao X, Shao M, Liu Y, Tong Z, Li W, Chinese Acute Pancreatitis Clinical Trials G (2020) Thymosin alpha 1 in the prevention of infected pancreatic necrosis following acute necrotising pancreatitis (TRACE trial): protocol of a multicentre, randomised, double-blind, placebo-controlled, parallel-group trial. BMJ Open 10:e037231

20. Balthazar EJ (2002) Acute pancreatitis: assessment of severity with clinical and CT evaluation. Radiology 223:603–613

21. Working Group IAPAPAAPG (2013) IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 13:e1-15

22. Sun JK, Li WQ, Ni HB, Ke L, Tong ZH, Li N, Li JS (2013) A modified gastro-intestinal failure score for patients with severe acute pancreatitis. Surg Today 43:506–513

23. Ke L, Ni HB, Tong ZH, Li WQ, Li N, Li JS (2012) D-dimer as a marker of severity in patients with severe acute pancreatitis. J Hepatobiliary Pancreat Sci 19:259–265

24. Bradley EL 3rd (1993) 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 128:586–590

25. Wang X, Zeng X, Yang B, Zhao S, Chen W, Guo X (2015) Efficacy of thymosin alpha1 and interferon alpha for the treatment of severe acute pancreatitis in a rat model. Mol Med Rep 12:6775–6781

26. Xue J, Sharma V, Habtezion A (2014) Immune cells and immune-based therapy in pancreatitis. Immunol Res 58:378–386

27. Gorelick FS, Lerch MM (2017) Do animal models of acute pancreatitis reproduce human disease? Cell Mol Gastroenterol Hepatol 4:251–262

28. Garg PK, Madan K, Pande GK, Khanna S, Sathyanarayan G, Bohidar NP, Tandon RK (2005) Association of extent and infection of pancreatic necrosis with organ failure and death in acute necrotizing pancreatitis. Clin Gastroenterol Hepatol 3:159–166

29. Wu J, Zhou L, Liu J, Ma G, Kou Q, He Z, Chen J, Ou-Yang B, Chen M, Li Y, Wu X, Gu B, Chen L, Zou Z, Qiang X, Chen Y, Lin A, Zhang G, Guan X (2013) The efficacy of thymosin alpha 1 for severe sepsis (ETASS): a multicentre, single-blind, randomized and controlled trial. Crit Care 17:R8

30. Ancell CD, Phipps J, Young L (2001) Thymosin alpha-1. Am J Health Syst Pharm 58:879–885

31. Rodriguez JR, Razo AO, Targarona J, Thayer SP, Rattner DW, Warshaw AL, Fernandez-del Castillo C (2008) Debridement and closed packing for sterile or infected necrotizing pancreatitis: insights into indications and outcomes in 167 patients. Ann Surg 247:294–299

32. Minkov GA, Yovtchev YP, Halacheva KS (2017) Increased circulating CD4+CD25+CD127low/neg regulatory T-cells as a prognostic biomarker in acute pancreatitis. Pancreas 46:1003–1010

33. Novotny AR, Reim D, Assfalg V, Altmayr F, Friess HM, Emmanuel K, Holzmann B (2012) Mixed antagonist response and sepsis severity-dependent dysbalance of pro- and anti-inflammatory responses at the onset of postoperative sepsis. Immunobiology 217:616–621

34. Simovic MO, Bonham MJ, Abu-Zidan FM, Windsor JA (1999) Anti-inflammatory cytokine response and clinical outcome in acute pancreatitis. Crit Care Med 27:2662–2665

35. Hotchkiss RS, Colston E, Yende S, Crouser ED, Martin GS, Albertson T, Bartz RR, Brakenridge SC, Delano MJ, Park PK, Donnino MW, Tidswell M, Mayr FB, Angus DC, Coopersmith CM, Moldawer LL, Catlett IM, Girgis IG, Ye J, Grasela DM (2019) Immune checkpoint inhibition in sepsis: a Phase 1b randomized study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of nivolumab. Intensive Care Med 45:1360–1371

36. Munir F, Jamshed MB, Shahid N, Hussain HM, Muhammad SA, Mamun AA, Zhang Q (2020) Advances in immunomodulatory therapy for severe acute pancreatitis. Immunol Lett 217:72–76

37. Johnson CD, Kingsnorth AN, Imrie CW, McMahon MJ, Neoptolemos JP, McKay C, Toh SK, Skaife P, Leeder PC, Wilson P, Larvin M, Curtis LD (2001) 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 48:62–69

38. Abu-Zidan FM, Windsor JA (2002) Lexipafant and acute pancreatitis: a critical appraisal of the clinical trials. Eur J Surg 168:215–219

39. Wang R, Yang F, Wu H, Wang Y, Huang Z, Hu B, Zhang M, Tang C (2013) High-dose versus low-dose octreotide in the treatment of acute pancreatitis: a randomized controlled trial. Peptides 40:57–64

40. Liu Y, Pan Y, Hu Z, Wu M, Wang C, Feng Z, Mao C, Tan Y, Liu Y, Chen L, Li M, Wang G, Yuan Z, Diao B, Wu Y, Chen Y (2020) Thymosin alpha 1 reduces the mortality of severe coronavirus disease 2019 by restoration of lymphocytopenia and reversion of exhausted T cells. Clin Infect Dis 71:2150–2157

41. Wu M, Ji JJ, Zhong L, Shao ZY, Xie QF, Liu ZY, Wang CL, Su L, Feng YW, Liu ZF, Yao YM (2020) Thymosin alpha1 therapy in critically ill patients with COVID-19: a multicenter retrospective cohort study. Int Immunopharmacol 88:106873

42. Gardner TB, Vege SS, Chari ST, Pearson RK, Clain JE, Topazian MD, Levy MJ, Petersen BT (2008) The effect of age on hospital outcomes in severe acute pancreatitis. Pancreatology 8:265–270

43. Weyand CM, Goronzy JJ (2016) Aging of the immune system. Mechanisms and therapeutic targets. Ann Am Thorac Soc 13(Suppl 5):S422–S428

44. Evans RP, Mourad MM, Pall G, Fisher SG, Bramhall SR (2017) Pancreatitis: Preventing catastrophic haemorrhage. World J Gastroenterol 23:5460–5468

45. Conway Morris A, Datta D, Shankar-Hari M, Stephen J, Weir CJ, Rennie J, Antonelli J, Bateman A, Warner N, Judge K, Keenan J, Wang A, Burpee T, Brown KA, Lewis SM, Mare T, Roy AI, Hulme G, Dimmick I, Rossi AG, Simpson AJ, Walsh TS (2018) Cell-surface signatures of immune dysfunction risk-stratify critically ill patients: INFECT study. Intensive Care Med 44:627–635

46. Gomatos IP, Xiaodong X, Ghaneh P, Halloran C, Raraty M, Lane B, Sutton R, Neoptolemos JP (2014) Prognostic markers in acute pancreatitis. Expert Rev Mol Diagn 14:333–346

47. Matta B, Gougol A, Gao X, Reddy N, Talukdar R, Kochhar R, Goenka MK, Gulla A, Gonzalez JA, Singh VK, Ferreira M, Stevens T, Barbu ST, Nawaz H, Gutierrez SC, Zarnescu NO, Capurso G, Easler J, Triantafyllou K, Pelaez-Luna M, Thakkar S, Ocampo C, de Madaria E, Cote GA, Wu BU, Paragomi P, Pothoulakis I, Tang G, Papachristou GI (2020) Worldwide Variations in demographics, management, and outcomes of acute pancreatitis. Clin Gastroenterol Hepatol 18:1567-1575 e1562

48. Tian X, Huang Y, Wang H (2017) Deviation of Chinese Adults' Diet from the Chinese Food Pagoda 2016 and Its Association with Adiposity. Nutrients 9

49. Li XY, Pu N, Chen WW, Shi XL, Zhang GF, Ke L, Ye B, Tong ZH, Wang YH, Liu G, Chen JM, Yang Q, Li WQ, Li JS (2020) Identification of a novel LPL nonsense variant and further insights into the complex etiology and expression of hypertriglyceridemia-induced acute pancreatitis. Lipids Health Dis 19:63