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EarLy elimination of fatty acids iN hypertriglyceridemia-induced acuTe pancreatitis (ELEFANT trial): Protocol of an open-label, multicenter, adaptive randomized clinical trial

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ABSTRACT

Introduction: Acute pancreatitis (AP) is a life-threatening inflammatory disease, with no specific pharmacological treatment. However, concerning some etiologies, early specific intervention (such as ERCP in biliary AP) has proven to be remarkably beneficial. Hypertriglyceridemia (HTG) induces severe pancreatic damage by several direct (cellular damage) and indirect (deterioration of microcirculation) mechanisms. Published data suggest that early removal of triglycerides (TGs) and toxic free fatty acids (FFAs) may be advantageous; however, high-quality evidence is still missing in the literature.

Methods: /Design: ELEFANT is a randomized controlled, multicenter, international trial testing the concept that early elimination of TGs and FFAs from the blood is beneficial in HTG-AP. The study will be performed with the adaptive "drop-the-loser" design, which supports the possibility of dropping the inferior treatment arm, based on the results of the interim analysis. Patients with HTG-AP defined by TG level over 11.3 mmol/l (1000 mg/dL) are randomized into three groups: (A) patients who undergo plasmapheresis and receive aggressive fluid resuscitation; (B) patients who receive insulin and heparin treatment with aggressive fluid resuscitation; and (C) patients with aggressive fluid resuscitation. Please note that all intervention must be started within 48 h from the onset of abdominal pain. Exclusion criteria are designed logically to decrease the possibility of any distorting effects of other diseases. The composite primary endpoint will include both severity and mortality.

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Results: Our null hypothesis is that early elimination of HTG and FFAs reduces the risk of mortality and severity of AP. Sample size calculation suggests that 495 patients will need to be enrolled in order to confirm or reject the hypothesis with a 10% dropout, 80% power and 95% significance level. The general safety and quality checks required for high-quality evidence will be adhered to. The study will be organized between November 2019 and October 2024.

Conclusion: Our study would provide the first direct evidence for or against early intervention in HTG-induced AP.

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Introduction

Acute pancreatitis (AP) is a life-threatening inflammatory disease, which can be induced by several different factors, such as alcohol, gallstones and fatty acids. Unfortunately, we do not have a specific therapy to treat AP generally; however, in some cases we can initiate specific interventions associated with one of the specific etiologies. Therefore, understanding our specific opportunities in each etiology of AP is crucially important.

From among the various etiologies, hypertriglyceridemia causes the most severe pancreatitis, and it is more likely that persistent organ failure can occur [1–5]. Its incidence rate is continuously rising due to worldwide changes in dietary habits and obesity as well [6]. In fact, hypertriglyceridemia-induced acute pancreatitis may explain almost one-third of cases of AP in certain populations [7]. Studies suggest that acute pancreatitis due to hypertriglyceridemia typically occurs when TG levels are >1000 mg/dL; >11.3 mmol/L [8,9]. Furthermore, the risk of acute pancreatitis is increased by 4% for every 100 mg/dL increase in TGs [10]. The assumed pathomechanism is the following: there are certain TG-rich lipoproteins, such as very low-density lipoprotein (VLDL) and chylomicrons. Chylomicrons are too large to penetrate the intimal surface of the endothelium and can cause an occlusion in pancreatic capillaries, leading to ischemia, acidosis and subsequently pancreatitis [11]. The second hit by triglycerides comes from their derivatives: hydrolysis of the TG components of these chylomicrons leads to free fatty acid (FFA) accumulation, which can cause cytotoxic injury to the pancreas. FFAs can injure the vascular endothelium, ductal and acinar cells in the pancreas by stimulating inflammatory mediators, releasing intracellular calcium, inhibiting mitochondrial complexes I and V, and causing necrosis and pancreatitis [12–18].

This cyclical FFA production can lead to rapid progression of pancreatitis. It is not surprising that therapies against these toxic mechanisms have already been tested. To break this cycle, it can be hypothesized that TG level should be rapidly reduced. One possible treatment modality is insulin. Insulin activates the lipoprotein lipase, which promotes the metabolism of chylomicrons and VLDLs [19]. The other effect of insulin is inhibition of the hormone-sensitive lipase, which would hydrolyze the TGs in the adipocytes to FFAs and would release them into the circulation [3]. Heparin also stimulates lipoprotein lipase (LPL) [20], which promotes the hydrolyzation of TGs to FFAs; however, heparin has no effect on hormone-sensitive lipase, so it may have worsened the lipotoxicity [18]. First, a rapid acceleration caused by heparin occurs at the level of lipoprotein lipase, which later turns into an opposite rapid decrease as a result of hepatic degradation. This deterioration promotes an incremental increase in chylomicron levels because of the depletion in the lipoprotein lipase plasma stores [3,21,22]. Therefore, heparin treatment in combination with insulin could be considered as a treatment option since it enhances LPL activity and is thus able to reduce serum TG and FFAs [23,24].

Plasmapheresis seems to be another effective therapeutic option, in which TG-rich plasma is removed through the apheretic machine [25]. Three different modalities of direct therapeutic plasmapheresis are available: (1) plasma exchange (PEX), (2) double filtration plasmapheresis (DFPP), and (3) immunoadsorption/plasma adsorption (IA/PA). During plasmapheresis, the blood is separated by a membrane plasma separator into plasma and cells. The separated plasma, which is loaded with pathogenic agents (TGs, in this case), is removed and replaced with a colloid solution, preferably albumin [26]. With regard to DFPP, after the plasma is isolated by a plasmaseparator, it is also fractionated by molecular weight. Components of large molecular weight (e.g. pathogenic substances) are eliminated while the small molecular weight components are returned to the patients (e.g. albumin). Less replacement fluid is needed during this procedure [27] in contrast to IA/PA, during which no substitution fluid is required at all. After the plasma is isolated by a plasma separator, it passes through an absorption column, which removes the pathogenic substances [28,29]. This kind of method is regularly used to eliminate antibodies [29,30]. Currently the only technique available in Hungary to eliminate all fatty acids is PEX. Plasmapheresis rapidly removes TGs and chylomicron from the circulation, removing the inciting factor and halting the further inflammation and damage to the pancreas. PEX lowers the lipid levels drastically within hours, compared to conservative therapy, that usually takes several days to achieve the same reduction in TG levels. Most patients require only one session of PEX, as it is reported, to lower TG levels by 50–80%. It has been postulated that PEX improves HTG-AP outcomes not only by lowering TG levels, but also by removing proinflammatory markers and cytokines to down-regulate the inflammatory process in HTG-AP [31,32].

However, no large multicenter, randomized clinical trials have been performed to demonstrate the evidence-based beneficial effects of these interventions. There are no guidelines available in pancreatology to treat HTG-AP; however, the recent American Society for Apheresis (ASFA) guidelines graded apheresis as 2C (weak recommendation; individualized decision is necessary, unclear role of therapy) in this condition. Other alternatives may be equally reasonable based on data from observational studies or cases series (category III evidence) [33]. Due to the paucity of randomized trials or high-quality comparator, no specific recommendations can be made, regarding the starting points or end points of PEX, but it seems reasonable to initiate the PEX in patients with HTG-AP as early as possible. Apheresis as a therapeutic modality needs stronger evidence, ideally in the form of a randomized clinical trial before consideration as a standard treatment strategy.

The main objective of this trial is to determine whether early elimination of TGs and FFAs from the blood is beneficial to patients with HTG-AP. Our null hypothesis is that early intervention reduces the risk of mortality and severity of AP (from 12.7% to 4.2%). To confirm this hypothesis, a randomized clinical trial involving all patients with HTG-AP is needed.

Methods

Design: ELEFANT is an international, multicenter, three-armed, randomized controlled clinical trial with the adaptive "drop-the-loser" design. This design allows dropping the inferior treatment arm, based on the result of the interim analysis. Patients with HTG-AP are randomized into three groups: (A) patients who undergo plasmapheresis and receive aggressive fluid resuscitation; (B) patients who receive continuous IV infusion of heparin combined with insulin (IHT) with aggressive fluid resuscitation; and (C) patients with aggressive fluid resuscitation.

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The study protocol was structured in accordance with Spirit 2013 [34].

Trial organization, committees and boards

The corresponding center and designer of the ELEFANT trial is the Center for Translational Medicine at the University of Pécs Medical School (coordinating institution and sponsor, www.tm-centre.org) and the Hungarian Pancreatic Study Group (HPSG-coordinating society, www.tm-centre.org). The HPSG was established in 2011 to strengthen research in pancreatology.

The following committees and boards will be involved:

The Steering Committee (SC) will be led by PH (principal investigator, gastroenterologist and specialist in internal medicine and clinical pharmacology). SC members from Pécs (HU) will be: NZ (physician and full-time employee on the project), ÁV (gastroenterologist and internist) and AH (hematologist and internist) and AS (interdisciplinary unit); Szeged (HU): LC (gastroenterologist and internist; Debrecen: (HU) MP (gastroenterologist and internist); Székesfehérvár (HU): FI (gastroenterologist and internist); and Békéscsaba (HU): MV (gastroenterologist and internist).Every centerwill have the opportunity to delegate one member to the SC. Additionally, there will be independent members as well. Furthermore, the SC will include a patient representative. Primary supervision of the study will be provided by the SC; it will make decisions concerning all important questions (e.g. premature termination of the study, dropouts etc.).

The International Translational Advisory Board (ITAB) will include three gastroenterologists (EM, VPS and JM) and a basic scientist (OHP). The task of the ITAB is to regularly monitor the trial and to provide recommendations to the SC.

The study was designed by the SC and ITAB. It was supported by the University of Pécs Medical School. The sponsor was not associated with the design of the trial and will have no access to the randomization codes or the data.

To comply with current ethical regulations, the study will have an independent physician and safety manager.

Study population

All patients with HTG-AP will be informed regarding the possibility of taking part in the ELEFANT trial. After signed informed consent, participants will be randomized into three groups if they meet all the inclusion criteria and no exclusion criteria (Fig. 1.).

Inclusion criteria

The inclusion criteria are: (1) age 18–80 years; (2) diagnosed AP on the basis of the "2 out of 3" criteria in the IAP/APA guidelines [35]: (a) upper abdominal pain; (b) serum amylase or lipase >3x upper limit of normal range; (c) characteristic findings on pancreatic imaging; (3) HTG is diagnosed: if the blood TG level is at least 1000 mg/dL (11.3 mmol/L); and (4) signed informed consent.

	STUDY PERIOD								
	Enrolment	Allocation	Post-allocation						Close-out
TIMEPOINT	*<48 hours**	0	*0h*	*6h*	*12h*	*24h*	*48h*	*72h*	*discharge*
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Laboratory test	X		X	X	X	X	X	X	X
Imaging (CT scan or US)	X								X
Allocation		X							
INTERVENTIONS:									
Plasmapheresis			←	—	→				
Insulin-heparin treatment			←	—	—	—	—	→	
Fluid therapy			←	—	—	→			
ASSESSMENTS:									
Questionnaire A		X							
Questionnaire B1,B2,B3			X	X	X	X	X	X	
Questionnaire C									X

*from the beginning of the abdominal pain

Fig. 1. Flow chart of participantsaccordingtothe SPIRIT 2013 statement.

Exclusion criteria

The exclusion criteria are: (1) pregnancy or breast feeding; (2) any of the interventions is not available within 48 h calculated from the start of abdominal pain; (3) any of the interventions can not be started within 12 h calculated from the venepuncture which provided the blood sample for HTG analysis (4) coma; (5) malignancy; (6) early ARDS; (7) renal failure; (8) allergy to insulin or heparin; (9) chronic pancreatitis; (10) hospitalization before admission; (11) any reasons contraindicating plasmapheresis: severe active bleeding or disseminated intravascular coagulation (hematocrit level $<20\%$), other forms of coagulopathy; hemodynamic instability; potassium plasma levels <3.5 mEq/L, sepsis, allergy to albumin, chronic heart failure (NYHA Grade II or more or ejection fraction lower than 50%) or symptoms of fluid overload at recruitment or long QT syndrome.

Sample size

Sample size calculation was based on a cohort analyses of 716 patients, of which 219 had elevated TG levels (unpublished data yet). Our data indicated that the combined rate of severe AP and mortality is significantly higher in HTG-induced AP vs. other etiologies of AP (12.7% vs. 4.2%, respectively). It is hypothesized that either plasmapharesis or IHT reduces HTG- and FFA-induced pancreatic damage with equal effectiveness. In order to detect this 66% relative risk reduction, it will be necessary to recruit a sample size of 495 subjects using a 10% dropout rate with 80% power at 95% significance level.

Time of randomization

Patients meeting all inclusion criteria and no exclusion criteria can be randomized after signed informed consent.

Randomization method

A randomization list will be generated by a computer program and will form the basis for numbered sealed envelopes containing the randomization information. After randomization, the data generated in the episode will be uploaded to the electronic case report form by the administrator.

Allocation will occur based on assembled randomization lists designed individually for each recruiting medical center. The Independent Data Management Board (IDMB) will prepare the sequence of distribution with variable block lengths with an allocation ratio of 1:1:1.

Blinding: Trial participants, care providers and outcome assessors will be blinded until the allocation to prevent patients being assigned to Groups A, B, and C. From assignment to intervention, blinding cannot be provided considering the study characteristics. The allocation sequence is blinded only to data analysts who are completely independent of the medical team (decision making) and data collection.

Study duration

The planned starting date of the study is January 2020, and the planned finishing date is December 2024.

Endpoints

Primary endpoint. The primary endpoint is a composite endpoint, which is based on the summation of cases with severe AP or mortality (this latter includes cases only with mild or moderate AP). All disease events are weighted equally. Severe AP is determined according to the revised Atlanta Classification (RAC) [36].

Secondary endpoints. The following secondary endpoints will be analysed: (1) serum TG level; (2) serum albumin level; (3) serum Ca level; (4) pain according to the visual analogue scale 1, 2 and 3 days after randomization; (5) C-reactive protein serum levels; (6) leukocyte count; (7) length of hospital stay; (8) need for ICU admission; (9) length of ICU stay; (10) organ failure (divided into transient and persistent organ failure according to the RAC definitions); (11) complications of plasmapheresis; and (12) cost calculation. Notably, only direct costs will be calculated, which include all medications, services, salaries of healthcare professionals, equipment and day care costs.

Intervention

In this study, plasmapheresis or IHT with aggressive fluid resuscitation will be the interventions. Patients will be randomized into Group A, B or C (Fig. 2.).

	STUDY PERIOD					
	Enrollment	Allocation	Post-allocation			
TIMEPOINT	*<48 hours**	0	*0h*	*6h*	*12h*	*24h*
ENROLLMENT:						
Eligibility screen	X					
Informed consent	X					
Laboratory test	X		X	X	X	X
Imaging (CT scan or US)	X					
Allocation		X				
INTERVENTIONS:						
Plasmapheresis			←	—	→	
Insulin-heparin treatment			←	—	—	—
Fluid therapy			←	—	—	→
ASSESSMENTS:						
Questionnaire A		X				
Questionnaire B1,B2,B3			X	X	X	X
Questionnaire C						

In Group A, patients will undergo plasmapheresis by plasma exchange after randomization (as soon as possible after admission). It is very important that the patients be hydrated before the procedure. Ringer's lactate will be administered with 5–10 mL/kg/h [37]. Of the three types of plasmapheresis noted above, we will use PEX.

Before the procedure the following items will be checked: 1. the blood test results (potassium, magnesium and total calcium, clotting parameteres). If the serum calcium level is low, calcium replacement

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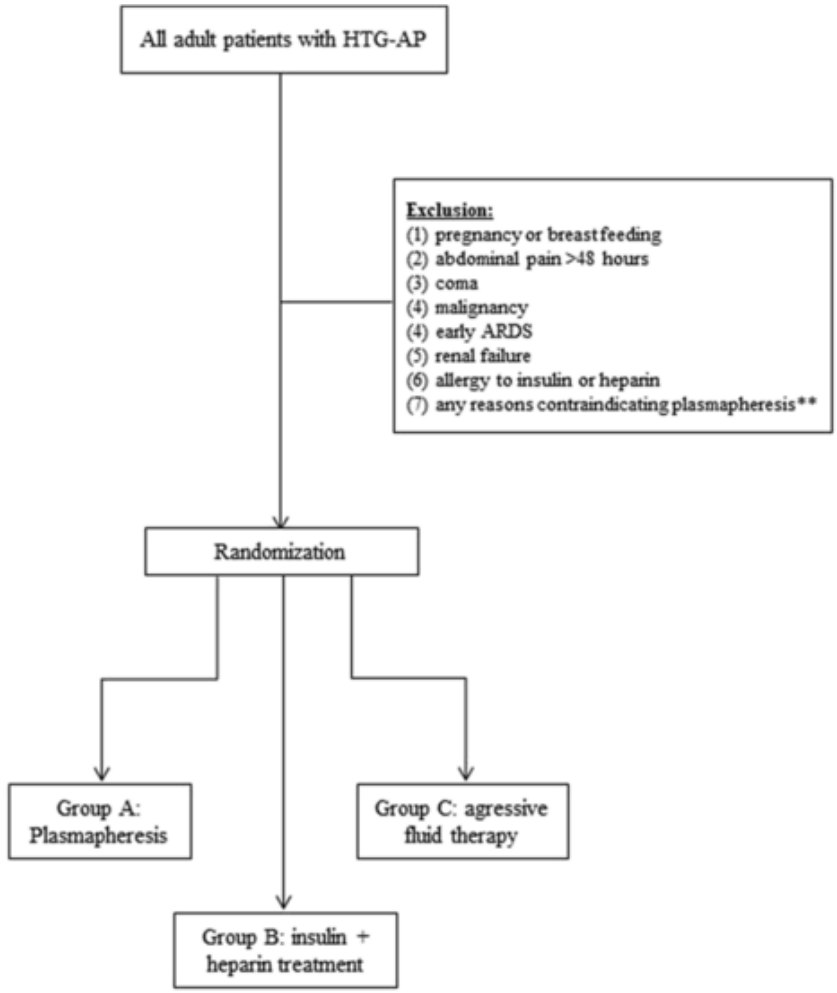
Fig. 2



**any reasons contraindicating plasmapheresis: severe active bleeding or disseminated intravascular coagulation (hematocrite level <20%), other forms of coagulopathy; hemodynamic instability; potassium plasma levels <3.5 mEq/L, sepsis, allergy to albumin, chronic heart failure (NYHA Grade II or more or ejection fraction lower than 50%) or symptoms of fluid overload at recruitment or long QT syndrome.

Schedule of enrollment, interventions and assessments according to the SPIRIT 2013 statement. Patients are randomized into three groups: (A) patients who undergo plasmapheresis and receive aggressive fluid resuscitation; (B) patients who receive insulin and heparin treatment with aggressive fluid resuscitation; and (C) patients with aggressive fluid resuscitation. Form A contains all of the parameters recorded on admission. The three B forms contains the information about the procedures (B1 – plasmapheresis, B2 – IHT, B3 – fluid therapy) and data, which are gathered every day during hospitalization. Form C contains data collected at discharge from the hospital.*from the beginning of the abdominal pain.

is necessary (aim is > 1 mmol/L). 2. get an accurate weight. After that the amount of plasma to be replaced will be calculated by the machine.

The intervention is usually carried out using an automated blood cell separator to ensure fluid balance and maintain a normal plasma volume. Patients will be administered a high flow central venous catheter. 1–1.5 plasma volumes (30–60 mL/kg) will be removed at each cycle. It will be replaced with isotonic 5.0% human albumin solution in order to avoid hyperalbuminaemia [38]. The amount of single blood volume is calculated by the machine based on sex, height, body weight and hematocrit level. Greater volumes can be exchanged at consultant discretion.

We will use citrate over heparin as an anticoagulant because literature data suggest that citrate is associated with lower mortality [39,40]. The colloid solution, with which the plasma will be replaced, will be two-thirds 5% human albumin and one-third physiological salt solution. There are no available studies which compare the replacement fluids. However, there is one review which reported that adverse events are more common when plasma is used instead of albumin [41].

Replacement flow rate can be increased to reduce the duration of the therapy. In patients receiving citrate anticoagulation, ionised calcium levels should be monitored and replaced periodically. Arterial blood gas, serum ionised calcium will be measured before and during the process, at 30 min, 1 h, 2 h and again hourly and at end of PE. We will administer 5 mL IV calcium to the patients continuously after every liter of plasma, because one of the frequently occurring adverse effects of plasmapheresis is numbness, which can be relieved by administering calcium.

After each cycle of plasmapheresis, we will measure the TG concentration. We will discontinue apheresis when the TG level is < 5.6 mmol/L. We will also check FBC and coagulation parameters post plasma exchange.

In Group B, patients will receive initial aggressive fluid resuscitation, just like in group A. An intravenous (IV) infusion of regular in-

sulin and a subcutaneous (SC) injection of low-molecular-weight heparin (LMWH) will be given, while closely monitoring the blood sugar level (every hour) and prothrombin time (PI) (every 12 h). If the blood sugar level is between 8.3 mmol/l and 11.1 mmol/l [3], we will administer 5% dextrose infusion to prevent hypoglycemia. The rate of insulin infusion will be 0.1 units/kg/hour, and the dose of LMWH (enoxaparin) is 4000 IU every 12 h. Published data suggest that IV insulin is more effective than subcutaneous insulin and it is much easier to titrate [42–44]. We will monitor the serum TG level every 12 h, and when it is normalized, IHT will be stopped.

In Group C, patients will receive just the aggressive intravenous fluid therapy. Please note that currently there are no evidence-based recommendations to treat HTG-AP.

Groups A, B and C will receive standard general treatment for AP based on the IAP/APA guidelines [37].

Monitored parameters during hospitalization

Laboratory tests and physical examinations will be performed on every patient every day during the hospital stay. TG level will be measured at the time of admission and right after the intervention, then 6,12,24,48,72 h after that. During IHT, blood sugar will be closely monitored (every hour), and prothrombin time (PI) will be determined every 12 h. In addition, a broad range of data will be assembled during the study (e.g. medical history, other laboratory tests (obligatory and recommended paramaters), diagnostic imaging, therapy and interventions, if necessary). Form A contains all of the parameters recorded on admission (Supplementary File 1). The three B forms contains the information about the procedures (B1 – plasmapheresis, B2 – IHT, B3 – fluid therapy) and data, which are gathered every day during hospitalization (Supplementary File 2, 3, 4). Form C contains data collected at discharge from the hospital (Supplementary file 5). Data collection on the case report form (CRF) will occur electronically (see Data management).

Discharge of patients

Uniformization of the length of hospital stay is necessary to avoid bias. Patients will be counted as discharged from the hospital/study when (1) oral feeding is tolerated for 24 h; (2) CRP level is < 50 mg/L; (3) abdominal pain has been completely resolved; and (4) no other pancreatitis-related complication requiring hospitalization is detected. Before the patient is discharged, either an ultrasonography (US) or computer tomography (CT) scan must be performed. A CT scan might be chosen if the result of the discharge US scan is uncertain or if local complications are predicted. In order to standardize US scans, sonographers will be instructed according to the trial requirements including the pre-defined assessment scheme (see form C) which usage is compolsury.

Data management and statistical analyses

Data handling

Data will be handled by the IDMB. Electronic CRFs (eCRFs) will be used. The Investigator will ensure that the data in the eCRFs are accurate, complete and legible. Detailed data flow will be described in a Data Management Plan (DMP). Data from completed eCRFs will be validated under the direction of the Data Manager on the IDMB according to a Data Cleaning Plan (DCP). Any missing, implausible or inconsistent recordings in the eCRFs will be referred back to the Investigator using a data query form (DQF) and will be documented for each individual subject before clean file status is declared. All changes to eCRFs will be recorded. Before Database Lock, the Data Review Meeting will decide and document necessary steps related to any issue in the database and define the analysis sets. Members of the Data Review Meeting are a delegated investigator, biostatistician and data manager. Adverse events will be coded using MedDRA in accordance with GCP, GLP, FDA 21CFR Part 11 and other relevant regulatory requirements.

Statistical analysis

Descriptive statistics – mean, median, standard deviation, quartiles and relative frequency – the χ^2 test, Z test with Bonferroni correction (categorical variables), relative risk (dichotomous variables), ANOVA (continuous variable) in the case of normal distribution, and Kruskal–Wallis test in the absence of a normal distribution will be performed. Affiliated statistical analyses will be performed with an error probability of 0.0294 (type I error probability).

Safety Analysis Set (SAS, all patients enrolled in the study), Per Protocol Set (PPS, all enrolled patients who finished the study conforming to the requirements of the study protocol) and Intention to Treat (ITT, all randomized participants who start on a treatment, excluding consent withdrawals) will be performed. Baseline patient and disease characteristics will be analysed using descriptive analysis. Demographic and baseline characteristics will be summarized for the overall study population. Descriptive statistics for both the primary and secondary parameters will be analysed similarly.

Withdrawal of a subject from PPS

Any participants/investigators and the IDMB can submit recommendations for dropouts from the PPS group with reasons provided to the SC. All recommendations will be filed. The SC will discuss all the information, and, if the alteration in the protocol is expected to have any bearing on the interventions and outcomes of the study, the patient will not be included in the final per-protocol analysis. Automatic dropout from the per-protocol group shall be ordered if: (1) any of the exclusion criteria are diagnosed during the course of AP; (2) parameters required for answering the primary endpoints are missing; (3) serious medical reasons not related to pancreatitis occur (e.g. accidents and stroke); or (4) a serious adverse effect occurs.

Premature termination of the study: In the interests of patient safety, an interim analysis will be conducted after 83 patients have completed the study in each treatment arm. We will calculate statistical power for the primary endpoints which will decide whether additional subjects should be enrolled. If no more subjects are needed, early stopping will be applied. We will test our hypotheses both in an interim and final analysis. For this reason, the p-value will be adjusted to diminish the probability of type I error. Therefore, the corrected level of significance (p-value) will be 0.0294.

The following rules will be applied:

1) If any of the groups are significantly ($p < 0.0294$) less effective than the others and it is already visible that there is no hope for ascertaining a significant difference between the other two groups, the study will be stopped.
2) If any of the groups are significantly ($p < 0.0294$) less effective than the others and it is already visible that there is hope of ascertaining a significant difference between the other two groups, the inferior treatment will be dropped and the study will be continued with the rest of the two arms only.
3) If any of the groups are significantly ($p < 0.0294$) more effective than the others, the study will be stopped.

The IDMB will perform an independent assessment of trial-related documents and activities with the aim of ensuring respect for subjects' right, safety and well-being and to guarantee the plausibility of clinical data. Similarity of groups at baseline will also be checked. The

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study will be discontinued if the difference between the planned number of patients and the actual number is higher than 60% within one year. The IDMB will report to the SC.

Centers: The trial will be launched in five Hungarian (Szeged, Debrecen, Pécs, Békéscsaba and Székesfehérvár) and 2 other European (Germany, Spain) centers. In addition, ELEFANT will be opened to other centers as well. In all cases, the IDMB will conduct an audit of the center and will report to the SC. The SC maintains the right to decide whether a center meets the required quality standards to join the study. The full protocol will be publicly available in an open access journal.

Publication policy: We would like to publish the results in an internationally highly recognized journal. Centerscan nominate an author after every 20 patients.

Patient and Public Involvement: This pre-study protocol contains no results and data; therefore, patients and or the public were not involved.

Safety

Although plasmapheresis is relatively safe, adverse events or serious adverse events can occur, and patients require careful observation during the procedure. Expected adverse events are listed below (see Table 1) [45]. Any change in the patient's status should prompt discontinuation of the PE procedure and evaluation of the cause of the symptoms. In this trial, the IDMB will examine safety variables after 30 patients have completed the study protocol. Moreover, investigators will report adverse or serious adverse events on a separate form, which must be sent to the IDMB and SC. The SC will discuss it, and, if the adverse effect is confirmed, it will be reported to the relevant institutional and national ethics committee (http://www.ett.hu/tukeb.htm).

Additional information and future plan

Blood samples (serum and plasma) from every patient will be stored. These samples can be used to analyse laboratory parameters later if required (e.g. due to an earlier failed measurement) and to build a biobank for future clinical studies. All the participants will be granted informed consent accordingly. The samples will be stored in a −80 °C freezer. A follow-up study (ELEFANT PLUS) is under construction to follow up patients for up to 5 years after enrollment in the study. We also intend to publish the study protocol.

Table 1
Overview of adverse events related to plasmapheresis.

Overview of adverse events	
Replacement fluid-related complications	Hypokalemia Hypocalcemia [a] Immunglobulin depletion Coagulation factor depletion
Citrate-related complications	Hypocalcemia Metabolic alkalosis Paresthesia Nausea Vomiting Chest pain Hypotension Tetany Arrhythmias
Vascular catheter-related complications	Infection Pain Nerve damage Thrombosis Dissecting hematoma Perforation Air embolism AV fistula

[a] The event rate for hypocalcemia will be collected; however, it cannot be determined whether hypocalcemia is an additional etiological factor or a complication of HTG-induced AP.

Discussion

HTG causes the most severe pancreatitis from among the different etiologies [1–5]. Preclinical research and clinical data suggest that FFAs, a TG derivative, are toxic agent which damage the pancreas through several direct (ATP depletion and mitochondrial damage) and indirect (ischemia) mechanisms [11–17]. Our main hypothesis is that elimination of FFAs from the blood improves the severity and mortality of HTG-AP. Literature data suggest that early removal of FFAs and TGs from the blood could be beneficial; however, there is no high-quality evidence for this statement [46]. ELEFANT is designed to provide the first evidence for or against early intervention in HTG-AP.

Declaration of competing interestCOI

There are no financial or other competing interests among the principal investigators (NZ and PH), the included patients or any member of the trial.

Authors' contributions

NZ, AH and PH constructed the trial. As associate members of the ITAB, EM, VPS, OHP and JM offered recommendations and will regularly follow the study. NZ, AH and PH outlined the manuscript, while all the authors edited the manuscript. AS and JA prepared the figures. The sample size calculation was carried out by NG. The treatments will be carried out by ÁV, IF, MP, LC, AM, IR and MV. NF will be responsible for the imaging. The final manuscript was reviewed and authorized by all of the authors.

Ethics and dissemination

Trial registration: The trial has been registered at the ISRCTNXXX.

Ethical approval: Scientific and Research Ethics Committee of the Hungarian Medical Research Council (XXXXXX).

Protocol Version: V1.0 01.08.2019.

Start of patient recruitment: Jan. 1, 2020.

Strengths and limitations

Strength 1: A randomized controlled, multicenter, international trial might provide the first direct, high-quality evidence for or against the need for and the type of early elimination of TGs and FFAs in HTG-induced AP.

Strength 2: The final conclusion can be drawn with an achievable number of patients (495) within a relatively short period.

Strength 3: The study enjoys continuous support from (i) an International Translational Advisory Board (ITAB), including top, well-established experts from various research fields, and (ii) an Independent Data Management Board (IDMB), which will handle the data separately.

Strength 4: Many centers have communicated their intention to participate in this study.

Limitation 1: Plasmapheresis should be available within 48 h of the onset of abdominal pain, thus possibly limiting the number of patients who can be enrolled.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.12.018.

List Of Abbrevations

AP	acute pancreatitis
HTG	hypertriglyceridemia
TG	triglyceride
FFA	free fatty acid
ITAB	International Translational Advisory Board
IDMB	Independent Data Management Board
VLDL	very low density lipoprotein
LPL	lipoprotein lipase
PE	plasma exchange
DFPP	double filtration plasmapheresis
IA/PA	immunoadsorption/plasma adsorption
ASFA	American Society for Apheresis
IHT	insulin – heparin treatment
HPSG	Hungarian Pancreatic Study Group
SC	Steering Committee
ARDS	acute respiratory distress syndrome
NYHA	New York Heart Association
RAC	Revised Atlanta Classification
ICU	intensive care unit
IV	intravenous
LMWH	low molecular weight heparin
INR	international normalized ratio
CRF	case report form
DMP	data management plan
DCP	data cleaning plan
DQF	data query form
SAS	safety analysis set
PPS	per protocol set
ITT	intention to treat

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