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Progress Report

Chronic use of statins and risk of post-ERCP acute pancreatitis (STARK): Study protocol for an international multicenter prospective cohort study

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ABSTRACT

Background: Acute pancreatitis (AP) is the most common complication after endoscopic retrograde cholangiopancreatography (ERCP). Statins have been traditionally associated to an increased risk of AP, however, recent evidence suggests that statins may have a protective role against this disease.
Aims: Our primary aim is to investigate whether the use of statins has a protective effect against post-ERCP pancreatitis (PEP). Secondary outcomes are: to evaluate the effect of other drugs on the incidence of PEP; to ascertain the relationship between the use of statins and the severity of PEP; and to evaluate the effect of other risk and protective factors on the incidence of PEP.
Methods: STARK is an international multicenter prospective cohort study. Centers from Spain, Italy, Croatia, Finland and Sweden joined this study. The total sample size will include about 1016 patients, which was based on assuming a 5% incidence of PEP among non-statin (NSt) users, a 1–3 ratio of statin (St) and NSt consumers respectively, a 70% decrease in PEP among St consumers, an alpha-error of 0.05 and beta-error of 0.20. All patients aged ≥18 years scheduled for ERCP will be offered to enter the study.
Discussion: STARK study will ascertain whether statins, a safe, widely used and inexpensive drug, can modify the incidence of PEP.

1. Rationale and aims

Endoscopic retrograde cholangiopancreatography (ERCP) is the main endoscopic therapeutic procedure used for pancreaticobiliary disorders. Acute pancreatitis (AP) is the most common complication after ERCP, with an incidence ranging 3.5–9.7%, and a mortality rate of 0.7% [1,2]. Numerous prospective studies and meta-analyses have identified several patient-related and procedure-related risk factors for post-ERCP pancreatitis (PEP), such as female gender, previous AP or PEP, normal serum bilirubin, high number of cannulation attempts and time needed for cannulation [1]. Several pharmacological agents have been investigated for the prevention of PEP [3,4]. Current European Society of Gastrointestinal Endoscopy guidelines recommend routine rectal administration of diclofenac or indomethacin immediately before or after ERCP in all patients and, in addition to this, the placement of a prophylactic

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pancreatic stent should be strongly considered in case of high risk for PEP [1].

3-Hydroxy-3-methyl-glutaryl-coenzyme A (HMG co-A) reductase inhibitors (statins) are effective and commonly used worldwide as a treatment for dyslipidemia [5], and increasing evidence shows that statins also have anti-inflammatory effects [5,6]. Earlier reports suggested a potential association of statins to an increased risk of AP, however, several recent studies have demonstrated that the use of statins may actually be a protective factor against AP [7–11]. A meta-analysis of randomized controlled trials suggested that the use of statins is associated with a lower risk of pancreatitis [9]. A large population-based study by Wu et al. [8] showed that simvastatin use was independently associated with a reduced risk of AP. A Danish population-based case-control study with 2576 first-time admitted cases of AP and 25,817 age- and gender-matched controls showed no increased risk of AP among statin users and hypothesized a protective effect [10]. Gornik et al. [11] reported that statin treatment reduced morbidity and mortality in patients with AP. Furthermore, a new meta-analysis of observational studies demonstrated that statin use is not associated with an increased risk of AP, however, more studies are needed to explore the effect of statins [12]. Promising results towards statin beneficial effect on AP have also been shown in preclinical studies [13,14]. Therefore, the relationship between use of statins and risk of pancreatitis should be re-examined considering a potential beneficial effect. The hypothesis of this study is that the anti-inflammatory effect of statins might actually reduce the incidence of PEP. Thus, our main objective is to investigate the association between the use of statins and the incidence of PEP.

2. Study design

The STatins and post-ERCP Acute pancreatitis RisK (STARK) study is an international multicenter prospective cohort study evaluating the effect of the use of statins on the risk of PEP. The study is carried out in Spain, Italy, Croatia, Finland and Sweden. This project is part of the Pancreas 2000 Educational Program. The study was approved by The Ethics Committee for Clinical Research of each participating center. The number of study approval is EMP-PARA-2017-01. The study follows the good clinical practice guidelines and the recommendations of the 2013 Declaration of Helsinki.

Inclusion criteria are the following: age $\geq$18 years and being scheduled for ERCP, in addition having signed the informed consent form. Patients unwilling to participate, with ongoing AP, with surgically-altered biliary anatomy (such as hepaticojejunostomy or choledocho-duodenostomy), with failure to reach the papilla and patients undergoing ERCP for only stent removal or exchange will be excluded. Independent variables recorded for the study include sex, age, weight, height, smoking habit, alcohol intake, diabetes and related medications, previous AP and features related to it, history of chronic pancreatitis (CP), use of statins (length of use, type, dose and time to last dose consumed), other medications [heparin, nonsteroidal anti-inflammatory drugs (NSAIDs), fibrates] taken by the patient, indication for ERCP and ERCP features such as previous ERCP with sphincterotomy, dilatation of extrahepatic bile duct, serum bilirubin, precut sphincterotomy, pancreatic sphincterotomy, failure to clear bile duct stones, intraductal ultrasound, operator experience, periprocedural hydration, biliary cannulation time and cannulation attempts, Wirsung cannulation or injection, peripapillary balloon dilation and type of sedation (Table 1).

PEP was defined according to the revised Atlanta classification as two of the following three criteria: (i) abdominal pain (acute onset of pain often radiating to the back); (ii) serum lipase or amylase at least three times the upper limit of normal range; and (iii) characteristic findings of acute pancreatitis on imaging [1,15]. No financial support is required for this observational study.

2.1. Study endpoints

2.1.1. Primary outcome

The main outcome is the incidence and relative risk of PEP among statin (St) and non-statin (NSt) users.

2.1.2. Secondary outcomes

Secondary outcomes are: the effect of other drugs on the incidence of PEP; the relationship between the use of statins and the severity of PEP; and the effect of risk factors (gender, previous pancreatitis, age, non-dilated extrahepatic bile duct, absence of CP, normal serum bilirubin, cannulation attempts duration, pancreatic guidewire passages and injection, precut sphincterotomy, pancreatic sphincterotomy, balloon dilation of biliary sphincter, failure to clear bile duct stones and intraductal ultrasound) and protective factors (rectal administration of diclofenac or indomethacin and placement of a prophylactic pancreatic stent) in the incidence of PEP.

2.2. Statistical methods

The total sample size will include about 1016 patients, which was based on assuming a 5% incidence of PEP among NSt users, a 1–3 ratio of St and NSt consumers respectively, and a 70% decrease of PEP rate among St consumers [1,8,16]. Alpha-error was set 0.05 and beta-error 0.20. The STROBE guidelines for observational studies will be followed to report our findings [17]. Data will be presented as mean (standard deviation), median (interquartile range) or number (%) as appropriate. All statistical tests will be 2-tailed, and P values of less than 0.05 will be considered statistically significant. The manuscript will contain the baseline characteristics of the patients and analysis of the primary and secondary outcomes of the study. The association between St users and PEP will be analyzed in univariate analysis by means of Chi-squared test and in multivariate analysis by means of binary logistic regression. Incidence, Odds ratio (OR) (95% confidence interval) and adjusted OR (aOR) will be used as measures of the frequency and strength of association of PEP among St and NSt users. The aOR will be calculated by means of binary logistic regression, using the following variables in the model: gender, age, previous pancreatitis, use of rectal diclofenac or indomethacin, previous ERCP with sphincterotomy, duration of cannulation attempts, pancreatic guidewire passages, pancreatic injection, precut sphincterotomy, pancreatic sphincterotomy, pancreatic duct stent placement and balloon dilation of biliary sphincter. The frequency and percentage of missing values for each variable will be collected, analyzed and reported (missing value analysis). All data will be anonymous once data collection is completed, respecting the confidentiality of the subjects participating, in accordance with data protection laws. Data monitoring was performed for the STARK study.

3. Discussion

AP can range from mild discomfort to fatal illness and little is currently known on how to prevent recurrent attacks. Many different drugs have been tested to prevent PEP. Statins are a safe, widely used and inexpensive group of drugs that have been associated to a decreased risk of AP in recent studies. If statins protect against AP, they could also have a protective role in the prevention of PEP. STARK study aims to find out whether statins can change the incidence of PEP. Positive results in this observational study will also justify future clinical trials aiming to determine whether statins are

Table 1
Data collection sheet.

STAtins and post-ERCP acute pancreatitis RisK

□Alicante (Spain)
□Rome (Italy)
□Milan (Italy)
□Helsinki (Finland)
□Rijeka (Croatia)
□Stockholm (Sweden)

Pt Initials _____ **Date** _____

Exclusion Criteria: *(if any selected, do not go ahead with the form, but keep this information)*
□ < 18 years of age □ Unwilling to participate
□ Ongoing acute pancreatitis*
□ Stent removal/exchange/clearing
□ Hepatico or choledoco-duodenostomy or jejunostomy
□ Impossibility to position the scope in front of the papilla

Patient characteristics:

□M □ F Age_____ Height (cm)_____ Weight (kg)_____ Race: _____
Smoke □ No □ Yes (□Active ___cigs/day □Ex≥6months) Alcohol □ No □ Yes (□Active ___U/day □Ex≥6months)
Diabetes □ No □ Yes (□None □insulin □ metformin □incretin) *(1U=125ml wine, 330 ml beer, 40 ml spirit)*
Other comorbidities: □ Coronary A. Disease □ Heart Failure □ Stroke □ Chronic Kidney Failure □ Respiratory Failure
Previous acute pancreatitis: □No □ Yes □ Unknown Chronic pancreatitis: □No □ Yes □ Unknown
How many _____ Etiology: □ biliary □ alcohol □ post-ERCP □ _____

Drugs:
Statins: □ No □ Yes

□ Atorvastatin (torvast, totalip)
□ Fluvastatin (lescol, lipaxan, primesin)
□ Lovastatin (lovinacor, rextat, tavacor)
□ Pravastatin (aplactin, prasterol, pravaselect, sanare, selectin)
□ Rosuvastatin (crestor, provisacor, simestat)
□ Simvastatin (liponorm, medipo, sinvacor, sivastin, zocor)
□ Simvastatin + ezetimibe (inegy, goltor, vytorin)

□5 mg □10 mg □20 mg □40 mg □60 mg □80 mg □100 mg
For how long? _____ (years)
When did you take your last pill? _____ days ago

Suppository:
□ Indometacin
□ Diclofenac

Heparin: □ No □ Yes
NSAIDs (other than suppository): □ No □ Yes
Fibrates: □ No □ Yes

Indication to procedure *(even more than 1)*:
□ acute cholangitis □ gallstone in bile duct □ biliary stenosis (□benign □ malignant □ unknown)
□ pancreatic stones □ pancreatic stenosis □ Wirsung rupture/fistula □ Pancreas Divisum
Other: _____

ERCP features: □ EUS+FNA prior to ERCP
Dilated bile duct: □No □ Yes Bilirubin: □ normal □ elevated (_____ mg/dl)
Diverticulum □No □ Yes Previous ERCP (with sphincterotomy) □No □ Yes
Operator: □Expert(>300 ERCPs) □Non-expert(<300 ERCPs) Procedure time: □< 20 min □>20 min (___ min)
Biliary cannulation: □Easy (< 5 min/≤5 contacts) □ Difficult (>5 min/>5 contacts) □Failure to cannulate
□ Through the papilla □ Pre-cut □ Infundibulotomy □Transpancreatic septotomy Balloon dilation □No □ Yes
Wirsung cannulations □≤1 □>1 Wirsung contrast injections □≤1 □>1
Insertion of stent: □No □ Yes (□ bile duct □ Wirsung)

Type of sedation: □ Midazolam □Propofol Intubation: □ No □ Yes
Hydration during the procedure: NaCl _____ ml Ringer Lactate _____ ml
Glucose _____ ml Other_____ ml

Post-ERCP Acute Pancreatitis:
□ No □ **Yes**
Definition: Typical symptoms + amylase/lipase > 3 upper limit of normal range

Other complications?
□ Bleeding
□ Perforation (□ duodenal □ biliary)
□ Cholangitis

Organ failure?* □No □ Yes
□ Heart (□ < 48 h □>48 h)
□ Lungs (□ < 48 h □>48 h)
□ Kidneys (□ < 48 h □>48 h)

ICU: □ No □ Yes
Inhospital mortality: □ No □ Yes (cause:_____)
Hospital stay (from PEAP to discharge): days

Local complications? □No □ Yes
□ Peripancr. fluid collection
□ Pancreatic pseudocyst
□ Acute necrotic collection
□ Walled-off necrosis
In case of necrosis: □ sterile □ infected

CT scan with contrast during admission? □No □ Yes

Severity:
□ mild — no organ failure and no local/systemic complication
□ moderate — any organ failure < 48 h or any local/systemic complication
□severe — any organ failure > 48 h

applicable for preventing PEP or recurrent attacks of AP in high risk patients.

Conflict of interest

None declared.

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