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A Randomized, Double-Blinded, Placebo-Controlled Trial of Simvastatin to Prevent Recurrent Pancreatitis

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To the Editor:

In a population-based cohort study of statin use and acute pancreatitis those taking simvastatin, the most commonly prescribed statin, experienced a marked reduction in acute pancreatitis incidence.[1] A pooled analysis of 16 randomized-controlled trials of statin with other disease endpoints reported a reduced risk of acute pancreatitis (risk ratio, 0.77;

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95% confidence interval, 0.62–0.97) in the statin-treated patients compared with placebo controls.[2] These data strongly support the hypothesis that statins attenuate pancreatitis.

We conducted a multicenter randomized, double-blinded, placebo-controlled, feasibility study to evaluate the effect of simvastatin treatment (40 mg) versus placebo on change in secretin-stimulated peak bicarbonate concentration in pancreatic fluid among patients with recurrent acute pancreatitis (RAP). Eligible participants were at least 18 years of age with at least two episodes of acute pancreatitis in the past 12 months using the Revised Atlanta Classification.[3]

Exclusion criteria included prior use or current statin use, systemic use of medications that may interfere with statins, history of chronic myopathy, pregnancy or breastfeeding, gallstones or hypertriglyceridemia that requires medical or surgical intervention, history of active malignancy in the past 2 years, and active infection with human immunodeficiency virus. Patients were also excluded with advanced chronic pancreatitis (CP) as determined by the following criteria: 6 or more out of 9 endoscopic ultrasound ductal and parenchymal criteria of CP; calcifications in combination with atrophy and/or duct dilation of ≥5 mm; or evidence of advanced CP (Cambridge 3 or 4) by computed tomography or magnetic resonance imaging results in the past 12 months.

Participating study centers included gastroenterology clinics at Cedars-Sinai Medical Center (Los Angeles. Calif), Kaiser Permanente/Southern California Permanente Medical Group (Los Angeles, Calif), the University of Pittsburgh Medical Center, and Stanford University. Patients were randomized (imbalanced randomization [2:1]) to 40 mg simvastatin or placebo daily for 6 months. Participants were asked to come to the clinic for a baseline visit, Study Visit 2 at 3 months, and Study Visit 3 at 6 months.

The primary outcome for this study was improvement in pancreatic function. The endoscopic pancreatic function test (ePFT) was used to measure the change in secretin-stimulated peak bicarbonate concentration in the pancreatic fluid from baseline to 6-month follow-up.[4,5] Secondarily, an ePFT was also administered at Study Visit 2 (Month 3) to examine trends in pancreatic function. Duodenal aspirates were collected under propofol sedation at different time periods following secretin stimulation (0–10, 10–20, 20–30, 30–45, and 45–60 minutes), and bicarbonate levels were measured to determine pancreatic duct cell reserves. An immune signature panel was performed by the Human Immune Monitoring Center at Stanford University (http://iti.stanford.edu/himc/protocols.html) using Luminex bead array kits (EMD Millipore Corporation, Burlington, Mass).[6]

Thirty-eight RAP patients were pre-screened as eligible for the trial and were approached; however, 30 patients (79%) were not enrolled. Six RAP patients (4 women, 2 men) were randomized to simvastatin and two patients (2 men) to the placebo control between 2016 and 2019. The trial was closed for failure to recruit a minimum 50% of the recruitment goal. The resulting sample size was too small to draw conclusions regarding the study endpoints. Barriers to recruitment included stringent eligibility criteria and high prevalence of statin use in the adult population of the United States. Gallstone disease, continued

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chronic alcohol abuse, and concern about the complex study procedures were important barriers to recruitment.

Mean peak bicarbonate levels did not differ significantly between the simvastatin and placebo groups ($P = 0.29$) in intention-to-treat-analysis (Table 1). After adjustment for treatment, visit, and treatment x visit interaction (P for interaction = 0.07) the difference remained nonsignificant. While none of the results achieved statistical significance, the peak bicarbonate concentration (mmol/L) between the baseline and 6-month visit tended to decrease in the simvastatin group (mean, −8.2 [standard deviation {SD}, 22.7]) but increase in the placebo group (mean, 5.5 [SD, 0.7]) (Table 1). The expression of three biomarkers, hepatocyte growth factor, Resistin, and Fas ligand were differentially expressed ($P < 0.05$) between the simvastatin and placebo groups (Table 1).

This feasibility study provides important insight regarding the design of future trials in subjects with RAP. The selection of ePFT as a primary outcome measure should be avoided. Alternative study endpoints need to be considered that are less invasive and more likely to attract patient interest in participation. To complement health-related quality of life outcomes like pain alleviation, the use of validated imaging or molecular markers of progression, such as circulating cell-free mitochondrial DNA,[7] must be further developed. Attainability of recruitment goals is an important consideration in future trials.

Conflicts of Interest and Source of Funding:

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TABLE 1.

Peak Bicarbonate Levels and Fluorescence Intensity for Biomarkers by Study Visit

	Placebo (N = 2)			Simvastatin (N = 6)		
	Baseline	**Month 3**	**Month 6**	**Baseline**	**Month 3**	**Month 6**
Peak bicarbonate level, mmol/L						
Mean (SD)	72.0 (9.9)	85.5 (14.8)	91.0 (15.6)	81.7 (23.4)	79.5 (17.9)	71.3 (18.0)
Median (IQR)	72.0 (68.5–75.5)	85.5 (80.3–90.8)	91.0 (85.5–96.5)	83.0 (69.5–89.8)	82.5 (73.3–91.2)	75.0 (72.0–79.5)
Least square mean * peak bicarbonate levels, mean (95% CI), mmol/L	49.5 (4.8–94.3)	63.2 (28.7–97.7)	75.6 (42.3–108.9)	64.7 (38.9–90.6)	63.3 (43.3–83.3)	55.9 (36.6–75.2)
Least square mean † fluorescence intensity for biomarkers, mean (95% CI)						
Hepatocyte Growth Factor	7.13 (6.25–8.01)	5.81 (5.13–6.48)	5.99 (5.18–6.80)	5.71 (5.20–6.22)	5.81 (5.42–6.20)	5.76 (5.29–6.23)
Resistin	13.79 (12.99–14.60)	12.85 (11.94–13.75)	12.94 (11.83–14.05)	12.39 (11.93–12.86)	12.50 (11.97–13.02)	12.45 (11.81–13.10)
Fas Ligand	4.99 (4.67–5.30)	5.08 (4.76–5.41)	4.83 (4.48–5.18)	4.83 (4.65–5.02)	4.77 (4.59–4.96)	4.82 (4.62–5.02)

* Model fit with treatment, visit, and treatment x visit interaction

† Mixed effects model with ID as random effect and treatment and visits as fixed effects

CI indicates confidence interval; IQR, interquartile range.