RISK OF PANCREATITIS WITH STATINS AND FIBRATES

Hypertriglyceridemia is a common cause of pancreatitis. Guidelines recommend triglyceride-lowering therapy for patients with severe hypertriglyceridemia (triglycerides >500 mg/dL) based on observational data suggesting that reduction in triglycerides will reduce risk of pancreatitis. However, evidence that statins and fibrates may be associated with a higher incidence of pancreatitis is accumulating. Several case reports and observational pharmacoepidemiologic studies have proposed that statins and fibrates are independently responsible for cases of pancreatitis. This issue of CLIPS briefly evaluates a recently published meta-analysis that discusses this possible correlation. If you need further information on this topic, please contact the Samford University Global Drug Information Service at (205) 726-2659.


Methods

- The purpose of this meta-analysis was to identify de novo development of pancreatitis independent of evidence-based risk factors (e.g., hypertriglyceridemia, cholelithiasis) among patients with normal or mildly elevated triglycerides receiving statins or fibrates in large randomized, controlled clinical trials. Data were obtained from MEDLINE, EMBASE, and Web of Science databases.
- Inclusion/exclusion criteria per trial varied, but each study evaluated the effects of statin or fibrate therapy on cardiovascular events in patients. Trials with fewer than 1000 patients were excluded from the meta-analysis.
- Data from placebo-controlled trials evaluating statins (n=153,414) and fibrates (n=40,162) were pooled to elucidate the incidence of pancreatitis. In addition, dose-comparison trials using moderate and intensive statin therapy (n=39,614) were evaluated to determine if the incidence of pancreatitis exhibited a dose-dependent pattern. Statins studied were simvastatin, pravastatin, lovastatin, rosvastatin, and atorvastatin. Fibrates studied were fenofibrate, gemfibrozil, simvastatin/fenofibrate combination therapy, and clofibrate.
- Endpoints were evaluated by assessing if pancreatitis was reported during the trial as an adverse event within the follow-up period. Methodology for collecting this data differed among trials. All reports regarding pancreatitis were included in these data regardless of suspected etiology.
- Risk ratios (RR) and 95% confidence intervals were calculated using a random-effects model meta-analysis. Heterogeneity across studies was assessed using the χ² and I² statistics. P<0.05 was considered statistically significant.

Results

- A total of 28 trials (21 statin and 7 fibrate) and 193,576 participants were included. Five statin trials were dose-comparison trials (intensive dose vs. moderate dose); all other trials were placebo-controlled. There was limited statistical heterogeneity present in the analysis (I²=0%) and no evidence of publication bias.
- Mean follow-up time was 4.3 years for the statin group and 5.3 years for the fibrates group. Mean patient age was 62.6 years. Baseline triglyceride measurements in the statin and fibrate trials ranged from 118 mg/dL to 187 mg/dL and 145 mg/dL to 184 mg/dL, respectively.
- Analysis of 16 statin vs. placebo trials revealed that 0.27% of participants developed pancreatitis (RR, 0.77; 95% CI, 0.62–0.97; P=0.03; number needed to treat =1175 over 5 years). In five intensive-dose vs. standard-dose statin trials, 0.39% of participants developed pancreatitis (RR, 0.82; 95% CI, 0.59–1.12; P=0.21). Pooled data from seven fibrate vs. placebo trials showed that 0.36% of participants developed pancreatitis (RR, 1.39; 95% CI, 1.00–1.95; P=0.053; number needed to harm = 935 over 5 years).
- In both the statin trials and the fibrate trials, regression analysis revealed no relationship between risk of pancreatitis and reduction of triglyceride levels at 1 year.

CONTINUED NEXT PAGE
Discussion

- Analysis of pooled data indicated that statin therapy does not increase the risk of pancreatitis and may further confer a protective effect in patients with normal or slightly elevated triglycerides, as shown by a risk ratio <1 that was both statistically and clinically significant. Results of the statin dose-comparison trials cannot exclude the possibility of no difference between intensive vs. moderate dose statin regimens in the incidence of pancreatitis, as the decrease in risk was neither statistically nor clinically significant. These findings suggest that the protective effect of statins against pancreatitis is not a dose-dependent effect.

- Although the risk ratio associated with development of pancreatitis in patients receiving fibrates indicated a potential for harm (RR, 1.39), this finding was not statistically significant (P>0.05); furthermore, the 95% confidence interval for the risk ratio encompassed the value of equality, indicating a lack of clinical significance.

- Fibrates are indicated for the treatment of severe hypertriglyceridemia (triglycerides >500 mg/dL) based on observational data suggesting that a reduction of triglycerides corresponds to a reduction in the risk of pancreatitis. The fibrate trials evaluated in this meta-analysis included a patient population with baseline triglyceride levels of 145–184 mg/dL; these patients do not represent the population at increased risk of pancreatitis. Therefore, the findings of this study should not be interpreted as pointing to a lack of efficacy of fibrates in the reduction of pancreatitis in patients with triglycerides >500 mg/dL.

- The clinical utility of this meta-analysis is limited by the overall low incidence of pancreatitis that may be attributed to the inclusion of a patient population that was inherently at low risk for pancreatitis due to their normal or slightly elevated baseline triglyceride levels. Another limitation is that incidence of pancreatitis was not the primary endpoint of the trials, and the methods for detection of pancreatitis varied among the trials.

Summary

- Therapy with statins or fibrates is not associated with an increased risk of developing pancreatitis in patients with normal or slightly elevated baseline triglyceride levels. Pooled data suggest that statins are associated with a reduction in the risk of pancreatitis in this population. However, these results should be considered hypothesis-generating; further studies are needed to determine optimal lipid-modifying therapy in patients with hypertriglyceridemia.