BRIEF ARTICLE

Effect of ezetimibe on the prevalence of cholelithiasis

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Abstract

AIM: To investigate the prevalence of cholelithiasis among patients treated with ezetimibe.

METHODS: A retrospective, case-control study based on computerized medical records from patients of the Clalit Health Services, Sharon-Shomron region, from 2000 to 2009. Patients 20-85 years of age, who had been treated with ezetimibe and statins or statins only for at least 6 mo, and who had an abdominal ultrasound were included in the study. Collected data included age, gender, ezetimibe treatment duration, presence of hypothyroidism or diabetes, and existence of cholelithiasis as determined by ultrasound. Excluded were subjects after gallbladder resection, with hemolysis, myeloproliferative or inflammatory bowel diseases, and those treated with ursodeoxycholic acid and fibrates. Patients treated with statins and ezetimibe (study group) were compared to patients treated with statins only (control group).

RESULTS: The study group included 25 patients and the control group 168. All patients in the study were treated with statins. The study group included 13 males (52%) and 12 females (48%), the control group 76 males (45%) and 92 (55%) females ($P = 0.544$). The groups did not differ in age (mean age: 68 ± 8 years, range 53-85 years *vs* mean age: 71 ± 8 years, range 51-85 years; $P = 0.153$) or in the rate of diabetic and hypothyroid patients [11 (44%) *vs* 57 (33%), $P = 0.347$ in the study group and 5 (20%) *vs* 23 (14%), $P = 0.449$ in the control group, respectively]. Patients in the study group were treated with ezetimibe for an average of 798 ± 379 d. Cholelithiasis was found in 4 (16%) patients in the study group and in 33 (20%) patients in the control group ($P = 0.666$).

CONCLUSION: Ezetimibe does not appear to influence the prevalence of gallstones.

INTRODUCTION

Cholelithiasis is one of the most common diseases of the digestive system in the developed world. Its prevalence according to ultrasound-based studies is estimated to be 18.8% in females and 9.5% in males. Cholesterol stones make up 80%-90% of the gallstones in the Western world[1-8].

A delicate balance exists in the bile between the con-

centration of cholesterol and its main solubilizers, bile acids and phospholipids. Once the carrying capacity of cholesterol is exceeded, it can crystallize and initiate the formation of gallstones[5].

The treatment of hyperlipidemia consists of the inhibition of the two cholesterol sources in the body. Statins reduce cholesterol synthesis by inhibiting the key enzyme hydroxy methylglutaryl coenzyme A reductase, while ezetimibe decreases intestinal cholesterol absorption[9-12].

Ezetimibe blocks the mucosal Niemann-Pick C1-like1 receptor (NPC1L1)[12-18]. This causes a decrease in cholesterol absorption from the small intestine[16,19-22], loss of cholesterol into the stool and a decrease in the amount of cholesterol delivered to the liver and bile, thereby reducing the amount of cholesterol available for the formation of gallstones. Human liver cells also express the NPC1L1 receptor, which is located on the canalicular membrane and retains cholesterol by preventing its loss into bile and stool[12,13]. Thus, an opposite effect on bile is expected: biliary cholesterol enrichment and the formation of crystals and stones may occur when the receptor is inhibited by ezetimibe[12].

A few recent studies have evaluated the effects of hypocholesterolemic medication on gallstone formation. One study addressed the role of the hepatocyte NPC1L1 receptor and its function in cholesterol absorption from the biliary tract[12,13]. Transgenic mice with Hepatic NPC1L1receptor over-expression had a 10-30 fold decrease in biliary cholesterol without any effect on phospholipids or bile acid concentration. Biliary and plasma cholesterol concentrations returned to normal when ezetimibe was added[12]. In another study, Altmann *et al*[13] evaluated the effect of ezetimibe on gallstone formation in gallstone-susceptible mice. Ezetimibe prevented the formation of gallstones by effectively reducing intestinal cholesterol absorption. In the same study, 30 d of ezetimibe treatment was reported to decrease the biliary cholesterol concentrations and cholesterol saturation index in overweight patients with and without gallstones. Another study reported fewer cholecystectomies among subjects treated with statins compared to those not treated with the drug[14].

The aim of this study was to evaluate the prevalence of cholelithiasis among patients treated with ezetimibe. Since ezetimibe is usually not prescribed as monotherapy, we addressed the question in patients treated with concomitant statins.

MATERIALS AND METHODS

This retrospective case-control study was based on a review of computerized medical records of patients in the Sharon-Shomron region of Clalit Health Services (CHS), the largest health maintenance organization in Israel (and the second largest in the world), from 2000 to 2009.

The demographic and clinical data of all CHS members are contained in a central computer. This database is automatically updated with hospitalizations, invasive procedures, laboratory and imaging results, prescribed and purchased medications and mortality data.

The study inclusion criteria were patients 20 to 85 years of age, taking statins or statins and ezetimibe, with abdominal ultrasound results that included the presence or absence of gallstones. Statin or statin and ezetimibe treatment must have begun at least six months prior to the ultrasound. Subjects after gall bladder resection, with hemolysis, myeloproliferative or inflammatory bowel diseases, and those treated with ursodeoxycholic acid and fibrates were excluded.

The extracted data included age, gender, ezetimibe treatment duration, comorbidity with diabetes mellitus or hypothyroidism and the presence of gallstones based on abdominal ultrasound.

Patients were eligible for the study regardless of the indication for the ultrasound. In cases where a patient had more than one ultrasound, the most recent result was considered. All the scans were reviewed by an experienced radiologist.

Patients treated with ezetimibe and statins were compared to a matched control group of patients treated with statins only, to evaluate the prevalence of cholelithiasis.

The work was approved by the ethics committee of our institution (Helsinki Committee, Meir Medical Center, Israel, approval No. 020-09).

Statistical analysis

Data from the study groups were analyzed using the Pearson χ^2 test or the Fisher's exact test (each when appropriate) for non-parametric data and t test for continuous parametric data.

RESULTS

The study group included 25 patients treated with statins and ezetimibe. The control group consisted of 168 patients treated with statins only. Clinical and demographic data are presented in Table 1.

There were 13 males (52%) and 12 females (48%) in the study group and 76 males (45%) and 92 (55%) females ($P = 0.544$) in the control group. The groups did not differ in age (mean age: 68 ± 8 years, range 53-85 years *vs* 71 ± 8 years, range 51-85 years; $P = 0.153$) or in the rate of diabetic and hypothyroid patients [11 (44%) *vs* 57 (33%), $P = 0.347$ in the study group and 5 (20%) *vs* 23 (14%), $P = 0.449$ in the control group, respectively]. The mean duration of ezetimibe treatment was 798 ± 379 d. All patients were treated with statins. In the study group: simvastatin in 6 patients, atorvastatin 8, rosuvastatin 7 and pravastatin 4.

Cholelithiasis was found in 4 study group patients; 1 taking simvastatin and 3 treated with atorvastatin. In the control group: simvastatin 119, atorvastatin 19, rosuvastatin 11, and pravastatin 17 patients. Among the control group, 28 of the 33 gallstone positive patients had been

Table 1 Demographic and clinical characteristics of the patient groups

Study parameters	Study group (statins + ezetimibe) (*n* = 25)	Control group (statins only) (*n* = 168)	*P* value
Male/female	13 (52)/12 (48)	76 (46)/92 (55)	0.544
Mean age (yr)	68 ± 8	71 ± 8	0.153
Co-morbidities			
Diabetes	11 (44)	57 (34)	0.347
Hypothyroidism	2 (20)	23 (14)	0.449
Ezetimibe treatment			
Mean period (d)	799 ± 379		
Range (d)	183-1540		
Patients with gallstones	4 (16)	33 (20)	0.666

Data are presented as mean ± SD or *n* (%).

treated with simvastatin, 4 with atorvastatin, and 1 with rosuvastatin.

No statistically significant difference was found in the prevalence of gallstones in the study group (4, 16%) compared to the control group (30, 20%), *P* = 0.666.

No statistically significant differences were found in the prevalence of gallstones when controlling for age. Among patients ≤ 65, gallstones were present in 2 (18%) in the study group compared to 8 (17%) in the control group, *P* = 0.619. Among patients older than 65 years of age cholelithiasis was present in 2 (14%) study group patients and 25 (21%) control group patients, *P* = 1 by Fisher's exact test.

DISCUSSION

The results of this study show that treatment with ezetimibe in addition to statin therapy did not influence the prevalence of cholelithiasis. We compared patients treated with ezetimibe and statins to those treated with statins only because ezetimibe, which is not effective when used as monotherapy [low-density lipoprotein cholesterol (LDL-C) reduction of only about 16%], is usually given in combination with statins to patients who do not reach the recommended LDL-C levels with statin treatment (where it provides an additional reduction of 25% in LDL-C levels)[16,19-25].

The study was initiated because of two contradictory findings concerning the effect of ezetimibe on bile composition and gallstone formation[12,13]. Temel *et al*[12] addressed the inhibition of the hepatic canalicular membrane NPC1L1 receptor, which absorbs cholesterol from the bile. Inhibition of the receptor increases biliary cholesterol levels and the possibility of gallstone formation. In contrast, Altmann *et al*[13] reported that ezetimibe treatment resulted in decreased cholesterol bowel absorption and a net change in the bile composition to a less lithogenic type, when used in a mouse model as well as in human subjects[13].

To date, it is not clear whether statin-ezetimibe treatment over time leads to an increase or decrease in the prevalence of gallstones. A recent study revealed that statin-treated patients had fewer cholecystectomies compared to patients who did not take statins[14]. However, that study did not address the presence of gallstones or ezetimibe treatment[14]. Our study showed that the combination of statin and ezetimibe did not affect gallstone formation. A possible explanation could be the fact that statin treatment reduces the prevalence of gallstones, which masks the effect of ezetimibe on cholelithiasis.

The study has limitations, including the small number of patients who received ezetimibe and lack of information regarding the presence of gallstones prior to treatment with ezetimibe. However, this lack of information was true for both study groups. Another possible weakness might be the duration of ezetimibe treatment. Nevertheless, a mean duration of over two years seems a reasonable period in which to assess both gallstone formation and dissolution.

In conclusion, adding ezetimibe to statin therapy did not affect the prevalence of gallstones compared to treatment with statins alone.

COMMENTS

Background

Hyperlipidemia treatment consists of the inhibition of the two cholesterol sources in the body. Statins reduce cholesterol synthesis by inhibiting the key enzyme hydroxy methylglutaryl coenzyme A reductase, while ezetimibe decreases intestinal cholesterol absorption. This study was initiated because of two contradictory findings concerning the effect of ezetimibe on bile composition and gallstone formation. To date, it is not clear whether statin-ezetimibe treatment over time leads to an increase or decrease in the prevalence of gallstones.

Research frontiers

When using a combination of a statin and ezetimibe for the treatment of hyperlipidemia, it is unclear whether statin-ezetimibe treatment leads to an increase or decrease in the prevalence of gallstones over time. In this study, the authors did not demonstrate a reduction in gallstone prevalence.

Innovations and breakthroughs

This study shows that ezetimibe in combination with a statin does not affect gallstone formation.

Applications

Despite promising data in animal models, ezetimibe seems to have no potential in treating human gallstone disease.

Peer review

This is a good descriptive study in which authors investigate the prevalence of cholelithiasis among patients treated with ezetimibe. It is a retrospective study with negative results, yet it does convey a logical reason for the study. Hence, it may be accepted as a short paper.

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