Ezetimibe-associated adverse effects: what the clinician needs to know

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Summary

Objective: Ezetimibe is a relatively new lipid lowering agent, which is indicated for the treatment of primary hypercholesterolaemia, either as monotherapy or in combination with other hypolipidaemic drugs. The objective of the present article was to review the side effects attributed to ezetimibe administration and discuss their possible underlying mechanisms. Moreover, we aimed to comment on the possible drug interactions of ezetimibe and present current guidelines regarding its safe use. Methods: Relevant articles were identified through a PubMed search (up to June 2007). Results: Compelling evidence from the majority of the data reviewed here showed that adverse effects associated with ezetimibe use are few and mild without having been associated with serious clinical outcomes. In most studies ezetimibe has not been associated with increased rates of myopathy or rhabdomyolysis, whether used alone or in combination with statins, although there have been some case reports of myopathy attributed to this agent. Moreover, ezetimibe has been associated with mild elevations of liver transaminases, mainly in combination with a statin. Other side effects are extremely rare. It should be noted, however, there are no long-term safety data or outcome studies for ezetimibe yet. Conclusions: Ezetimibe is a safe alternative option for hyperlipidaemic patients intolerant to other lipid lowering drugs as well as a beneficial supplementary agent for patients who do not reach the recommended serum cholesterol level with their current hypolipidaemic treatment. However, as is the case with all new medications, physicians should be alert to recognise adverse effects associated with ezetimibe and report them to regulatory authorities.

Introduction

Hypercholesterolaemia is a well-established risk factor for cardiovascular disease (CVD), the leading cause of death worldwide (1–3). Since the introduction of statins, the mainstay of cholesterol lowering therapy, a great reduction of serum cholesterol levels can be achieved (4). However, there is still an important percentage of patients who do not reach their treatment goals or are statin intolerant (5). Therefore, new lipid lowering drugs, used alone or in combinations, are of great clinical significance. Ezetimibe has a different site of action from other currently available hypolipidaemic medications, aiming at cholesterol absorption in the gastrointestinal system. Thirty per cent of daily intestinal cholesterol comes from dietary sources, 50% from biliary content and 20% from sloughing of epithelial cells (Figure 1) (6). Ezetimibe selectively inhibits cholesterol absorption in the intestine by blocking the Niemann-Pick C1-like 1 (NPC1L1) protein cholesterol transporter (7,8). NPC1L1 is found at the brush border membranes of enterocytes and plays an important role in the absorption of intestinal cholesterol (7). The ezetimibe-induced inhibition of cholesterol absorption leads to a decrease in cholesterol delivery to the liver, resulting in reduction of hepatic cholesterol stores and subsequent increased cholesterol clearance from the blood. It is noteworthy that ezetimibe does not affect the absorption of triglycerides (TG), lipid-soluble vitamins or concurrently administered medications (9), thus exhibiting a more favourable adverse event profile compared with other lipid lowering drugs which act at the gastrointestinal system (cholestyramine, colestipol, colesavemal). Ezetimibe has been proved effective in cholesterol lowering, especially when being co-administered with other lipid lowering drugs (10–26). Ezetimibe is generally well...
tolerated, demonstrating an excellent safety profile (10,11,15,17–19,24). Side effects have been infrequently reported, mainly in combination treatment with statins (27–33). However, there are no long-term safety data or outcome studies for ezetimibe yet.

The aim of the present article is to summarise the adverse effects attributed to ezetimibe and elucidate their possible underlying mechanisms.

Methods

We searched the PubMed up to June 2007 using combinations of the following keywords: ezetimibe, adverse effects, side effects, muscle, myopathy, liver, hepatotoxicity, cholelithiasis, gallstones, lithogenicity, gastrointestinal, pancreatitis, sexual dysfunction, erectile dysfunction, libido, impotence, neuropathy, renal disease, proteinuria, thrombosis, cancer, arthritis, autoimmune diseases, skin, rash, eye, cataract, central nervous system, fatigue, dizziness, insomnia, headache, suicide, gynaecomastia and hair loss.

Randomised controlled trials, original papers, review articles and case reports with ezetimibe are included in the present review. References of these articles were scrutinised for relevant articles.

Effectiveness of ezetimibe in clinical trials

Several clinical studies evaluating the effectiveness and safety of ezetimibe, alone or in combination with other lipid lowering drugs, have been conducted (10–21). Ezetimibe has been associated with significant reductions in low-density lipoprotein (LDL) cholesterol in ezetimibe/statin combinations (10–12,14–16) and in combined ezetimibe/fenofibrate treatment (13,21). Ezetimibe also results in significant LDL cholesterol reductions as add-on therapy in patients already treated with colesvelam (19) or niacin (18) and in combination treatment with both simvastatin and fenofibrate (20). Moreover, ezetimibe combined with simvastatin (10), fenofibrate (13,21) or both (20) has been related to greater TG reductions compared with either of the above treatments. Moreover, ezetimibe has been linked to significant HDL cholesterol elevation in combination treatment with simvastatin (10), fenofibrate (21) or both (20). None of the aforementioned studies related ezetimibe to clinically significant side effects or drug intolerance. In studies where combination treatment of ezetimibe with a statin was compared with ezetimibe monotherapy the reported incidence of adverse effects was similar between the two groups (10,11,15).

A few studies have investigated the efficacy and safety of ezetimibe in the kidney transplant population (34–37). Renal transplant recipients often have elevated cholesterol levels despite statin therapy (38,39) and as CVD is the primary cause of death in these patients (40,41), complementary lipid lowering treatment is often warranted. Ezetimibe has been proved an effective and safe treatment option for dyslipidaemia, both in combination with statins and as monotherapy, in this group of patients (34,37).

There is only one study in the literature that evaluated the effects of combined ezetimibe/plant sterol treatment on plasma lipid levels (42). This study indicated that the combination treatment had no benefit over ezetimibe monotherapy in individuals with mild hypercholesterolaemia (42).
Ezetimibe and side effects

Muscle toxicity

Most lipid lowering drugs, including statins, fibrates and niacin, may cause muscle toxicity. In contrast, ezetimibe has not been associated with increased rates of myopathy or rhabdomyolysis, whether used alone or in combination with statins (43,44). In fact, the incidence of creatine kinase (CK) elevation with ezetimibe monotherapy is rather low (0.2%) and not different from that seen with placebo (0.1%) (45) or statin monotherapy (0.4%) (14,43–57). Furthermore, a recent extensive pooled safety analysis which involved 17 randomised clinical trials and 4558 patients suggests that ezetimibe does not enhance or aggravate statin-related myotoxicity (58).

On the other hand, there have been several case reports of myopathy attributed to ezetimibe (28–31,33,59). Fux et al. (28) described two patients with elevated CK activity after ezetimibe was added to statin therapy (atorvastatin and fluvastatin, respectively). In the first patient, after withdrawal of both drugs CK activity normalised and the patient’s symptoms (pain in both thighs and Achilles tendons) subsided, while reintroduction of atorvastatin did not induce any symptoms or biochemical abnormalities. In the second patient, elevated CK activity decreased and gradually returned to normal after withdrawal of ezetimibe, whereas fluvastatin was not discontinued. Simard et al. (30) described a case of a man who developed muscle pain and CK elevations when ezetimibe was added to atorvastatin. A similar case of atorvastatin/ezetimibe-induced myopathy with muscle pain and increased CK activity was reported by Weffald et al. (31). Again, ezetimibe withdrawal led to pain resolution and CK normalisation. Although neither patient in the aforementioned case reports was rechallenged with ezetimibe, concern about a potential pharmacokinetic interaction between ezetimibe and statins has been raised. The underlying mechanism might be glucuronidation (60), as most statins are not only hydrolysed by the cytochrome P450, but are also metabolised by glucuronidation; ezetimibe undergoes glucuronidation as well. Another candidate site of interaction might be organic anion transporting polypeptide type 2 (OATP2), of which several statins are substrates (61). OATP2 belongs to the OATP family. The role of these proteins is to clear organic anions from the various organs in which they are expressed. OATP2 differs in several properties from the other members of this family, as it is exclusively expressed in liver and is the only subtype which transports statins (61). Polar organic hydrophilic compounds require specific carriers for hepatic uptake, whereas lipo-philic compounds can freely permeate the basolateral hepatocyte membrane. Although lipophilic compounds do not need specific uptake mechanisms, they can act as substrates for transporters and potentially alter the hepatic handling of other drugs or endogenous compounds (62). Supposing that ezetimibe might also be a substrate of OATP2, a lipophilic statin could influence the hepatic handling of ezetimibe. However, the area under the curve for ezetimibe and statin co-administration does not support a significant increase in statin serum levels (14,63), challenging a pharmacokinetic interaction between the two drugs. Phillips et al. (29) suggest an interaction between ezetimibe and statin-associated myopathy, proposing defects in fatty acid (FA) oxidation as the possible underlying pathology. The same investigators identified a group of lipid lowering drug-intolerant patients with common features, which have been related to impaired FA oxidation (64–66). Ezetimibe could possibly impair FA oxidation and this may explain the ezetimibe-induced muscle side effects.

Ezetimibe has been reported to worsen myopathy in a patient with McArdle disease (33), the most common disorder of muscle carbohydrate metabolism, caused by mutations in the gene encoding myophosphorylase (67). In that report, 4 weeks after ezetimibe initiation the patient reported severe weakness, a prominent CK elevation occurred and slight myoglobinuria was diagnosed (33). When ezetimibe was discontinued, the patient recovered uneventfully and CK activity eventually returned to previous values. Although McArdle disease is a known cause of rhabdomyolysis, the present case suggests that myopathy may be aggravated by ezetimibe. However, as the patient was not rechallenged with ezetimibe, a definite cause-and-effect relation could not be established.

Finally, two recent case reports have linked ezetimibe monotherapy to myopathy (30,59). Simard et al. (30) described a case, in which a woman treated with ezetimibe developed muscle pain accompanied with CK elevation on two occasions, one with 10 mg and one with 5 mg of ezetimibe after a washout period. The recurrence of symptoms and biochemical alterations after the washout supports the hypothesis that ezetimibe alone can be associated with myotoxicity. If this is the case, the underlying pathology has not yet been elucidated and only plausible explanations have been suggested. These include cholesterol deficiency with secondary abnormal membrane function, disturbances in intracellular protein messaging caused by prenylated protein abnormalities and coenzyme Q10 deficiency leading to mitochondrial respiratory dysfunction (68).
Liver toxicity

Ezetimibe has been shown to cause elevations in liver transaminases, although clinically insignificant with monotherapy. Specifically, the incidence of consecutive elevations in serum transaminases (≥ 3 times ULN) has been found to be similar between ezetimibe (0.5%) and placebo (0.3%) (14,43–57). Moreover, no significant changes in conjugated bilirubin levels have been reported, thus excluding a major drug-related hepatocellular injury (68). Moreover, of the observed increased transaminase activity (≥ 2 times ULN) cases, most of them were isolated and reversible without apparent clinical significance. The underlying mechanisms by which elevations in liver enzymes occur with ezetimibe therapy remain unknown.

Co-administration of ezetimibe with a statin has been associated with increased incidence of consecutive elevations in serum transaminases (≥ 3 times ULN) (1.3% for ezetimibe/statin treatment vs. 0.4% with statins alone) (47–50,52–56), which appear to be related with statin dose. However, neither ezetimibe monotherapy nor combination treatment have been related to liver failure, need for liver transplantation or death.

Ezetimibe is primarily metabolised in the small intestine and liver (68). In patients with hepatic insufficiency its bioavailability increases (63). Current recommendations support the use of ezetimibe, even without dosage adjustment, in patients with mild, but not moderate or severe, hepatic insufficiency (68). The combination of ezetimibe with a statin is contraindicated for patients with active liver disease or unexplained persistence of serum transaminase elevations (68).

There are a few case reports in the literature attributing liver injury to ezetimibe (32,69,70). Stolk et al. (69) studied two patients with severe hepatic side effects in a general community hospital and described these patients as ezetimibe-induced severe cholestatic hepatitis and acute autoimmune hepatitis, respectively. Van Heyningen (70) presented a patient who developed acute hepatitis 3 months after starting on ezetimibe. The biochemical, immunological and histological findings demonstrated a drug-induced lupus-like autoimmune hepatitis. The time course suggests that ezetimibe may have acted as a trigger for autoimmune hepatitis. However, the patient had a history of thyroid autoimmune disease and was already on many long-term medications. Therefore, a definite association between liver injury and ezetimibe could not be established. Liu et al. (32) reported a patient with drug-induced biopsy confirmed liver injury 6 months after ezetimibe introduction in a woman without history of liver disease. Discontinuation of the drug resulted in amelioration of liver function tests. Drug-induced liver injury is the result of the formation of hepatotoxic reactive metabolites, often involving the cytochrome P450 system. The latter is not affected by ezetimibe, excluding it as a possible site of action for this case of drug-induced liver injury. As already mentioned, ezetimibe inhibits cholesterol absorption from the gut by acting on a sterol transporter, the NPC1L1 (7). As the human liver expresses this transporter protein, ezetimibe may also act on the liver (71). Ezetimibe and/or its metabolites may be toxic to hepatocytes in genetically predisposed individuals, as drug-induced liver injury usually develops in this group of people (32). Drug-induced hepatitis is frequently associated with antibodies directed against hepatic drug metabolising enzymes (72). Specifically, cytochromes P450 and uridine-diphosphate glucuronosyltransferases (UGTs) are targets of autoantibodies in several hepatic and extrahepatic autoimmune diseases (72). Possible ezetimibe induction of hepatic UGTs may stimulate autoantibody production against these target proteins, a mechanism suspected to be the cause of autoimmune-like hepatitis in the combined statin/ezetimibe therapy case (see above) (70).

Other adverse effects

Acute pancreatitis was recently described in a woman 2 weeks after ezetimibe was added to her usual simvastatin therapy (27). The clinical presentation and the laboratory test results were typical of acute pancreatitis. As other medical conditions were excluded and no change in the patient medications other than the addition of ezetimibe had occurred, acute pancreatitis was attributed to ezetimibe. After ezetimibe discontinuation the patient improved clinically and the altered biochemical profile gradually normalised. Although the investigators do not suggest a specific underlying pathophysiology, the timeline of events in association with the temporal administration of ezetimibe support a possible causal relationship between ezetimibe and acute pancreatitis. However, as acute pancreatitis has also been associated with statins (73,74), this could also be attributed to statin therapy.

A rather interesting and unusual case of hyperlipidaemia induced by ezetimibe has been reported (75). A 58-year-old woman with familial combined hyperlipidaemia/familial dyslipidaemic hypertension was started on ezetimibe therapy because of intolerance to several statins and fibrates. Soon after ezetimibe introduction, patient’s lipid profile deteriorated
Ezetimibe and side effects

As noncholesterol-lowering drugs, ezetimibe and other drugs. The major metabolic pathway for ezetimibe consists of glucuronidation of the 4-hydroxyphenyl group by uridine 5'-diphosphate-glucuronosyltransferase isoenzymes to form ezetimibe-glucuronide in the intestine and the liver (83).

Ezetimibe had no significant effect on a series of drugs (caffeine, dextromethorphan, tolbutamide and intravenous midazolam) known to be metabolised by cytochrome P450 1A2, 2D6, 2C8/9 and 3A4) in a 'cocktail' study of 12 healthy adult males (84). This indicates that ezetimibe is neither an inhibitor nor an inducer of these cytochrome P450 isozymes and is unlikely to affect the metabolism of drugs that are metabolised by these enzymes (84). Moreover, concomitant administration of ezetimibe with digoxin, triphasic oral contraceptives, cimetidine, antacids or glipizide had no significant effect on ezetimibe bioavailability (83).

**Cholestyramine**

Co-administration of ezetimibe with cholestyramine significantly decreased ezetimibe bioavailability. Hence, ezetimibe and cholestyramine should be administered several hours apart to avoid attenuating the efficacy of ezetimibe (83).

**Warfarin**

Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of 12 healthy adult males. However, there have been postmarketing reports of increased international normalised ratio (INR), mainly in patients who were also on other medications, with co-administration of ezetimibe and warfarin. It is recommended, therefore, that INR be appropriately monitored in such patients (84).

**Fibrates**

Co-administration of ezetimibe with fibrates other than fenofibrate has not been studied in clinical trials. In a study of 32 hypercholesterolaemic patients, concomitant treatment with fenofibrate increased the mean peak plasma concentrations and area under the curve values of ezetimibe approximately 64% and 48%, respectively (84). Moreover, in a 48-week study of 576 patients with mixed hyperlipidaemia treatment with fenofibrate was related with performed cholecystectomies in 0.4% of patients in this group compared with 1.2% in the fenofibrate/ezetimibe co-administration group. Although the difference between the two groups was not statistically significant, it might have reached significance in a larger study (63). Gemfibrozil has been found to increase
ezetimibe concentrations approximately 1.7-fold in a pharmacokinetic study (84). Although there is no clinical data regarding concomitant therapy with ezetimibe, the risk of adverse effects with gemfibrozil may be higher than that of other fibrates because gemfibrozil is the only fibrate which shares the same metabolic pathway with ezetimibe (glucuronidation). Therefore, co-administration of ezetimibe with fibrates other than fenofibrate is not recommended. Furthermore, in a patient with a high risk for cholelithiasis it is prudent to avoid concomitant use of ezetimibe with any fibrate.

Recommendations to healthcare professionals regarding ezetimibe therapy

The latest statement on lipid lowering drugs and muscle and liver safety put forth by the Office of Health Promotion and Disease Prevention has been recently published (68). These practice recommendations on ezetimibe muscle and liver safety represent an expert committee opinion and are briefly presented herein (Boxes 1 and 2).

**Ezetimibe and children**

The latest American Heart Association Scientific Statement provided recommendations for drug therapy of children and adolescents with high-risk lipid abnormalities (85). Data related to ezetimibe use in children are reported here.

Ezetimibe is regarded an important adjunctive hypolipidaemic agent in patients with familial hypercholesterolaemia (FH) who do not manage to reach their treatment goals with statin monotherapy (86,87). However, no trials of ezetimibe have been conducted exclusively in children, although ezetimibe/statin studies are currently in progress in children with heterozygous FH. One study of 50 patients with severe LDL cholesterol elevations because of homozygous FH included an unspecified number of children ≥ 12 years old (86) and demonstrated a favourable safety profile for combined ezetimibe/statin treatment. Current recommendations do not clarify a specific age at which ezetimibe is considered safe to be initiated (85).

**BOX 1: Recommendations on ezetimibe and muscle safety (68)**

- Obtaining a pretreatment baseline CK level before initiating ezetimibe therapy, either alone or in combination with a statin, is considered necessary only in patients who are at risk for suffering muscle toxicity (e.g. old individuals, combined ezetimibe/statin treatment with other potent myotoxic agents, such as the fibrates).
- CK measurements are required in symptomatic patients to assess the severity of myopathy and decide on a possible discontinuation or down-titration of ezetimibe.
- Discontinuation of ezetimibe therapy because of increased CK levels should take place only after other causes of CK elevation have been ruled out. When symptoms resolve, rechallenge with ezetimibe will either confirm or exclude their reproducibility.
- If patients on ezetimibe/statin therapy develop tolerable muscle symptoms or CK elevations < 10 ULN, the statin dose may be reduced or remain unaltered, while severity of symptoms should serve as the clinical guide to stop or continue treatment. On the other hand, if patients suffer from severe muscle complaints the statin should be either reduced or discontinued until symptoms resolve. Then the same or another statin, at the same or lower doses, can be restarted to assess the reproducibility of symptoms. Finally, if rhabdomyolysis (CK elevation > 10,000 IU/l or CK elevation > 10 ULN with an elevation in serum creatinine or requiring intravenous hydration therapy) occurs, both drugs should be discontinued and intravenous hydration in a hospital be instituted promptly. The most important recommendation is to encourage patients to report any adverse effects (e.g. pain, tenderness or weakness).

**BOX 2: Recommendations on ezetimibe and liver safety (68)**

- Although ezetimibe monotherapy has not been related to significant liver enzyme elevations, it is advisable to obtain pretreatment liver transaminase levels as a routine general evaluation of the patient.
- In combined statin/ezetimibe therapy transaminase levels should be measured both before initiation of the drugs and periodically thereafter.
- In patients with mild hepatic insufficiency no dosage adjustment is required. However, in moderate or severe hepatic insufficiency ezetimibe is contraindicated because of lack of evidence on long-term ezetimibe exposure in such patients.

Ezetimibe and children
Conclusions

As hypercholesterolaemia comprises a major risk factor for CVD, the achievement of LDL cholesterol target levels is of great clinical significance. Ezetimibe is a novel lipid lowering drug with a mechanism of action different from that of statins. Randomised controlled trials have confirmed the efficacy and safety of ezetimibe, both in monotherapy and in combination treatment with other hypolipidaemic drugs. Side effects have been described, but they were usually mild and reversible with or without cessation of the drug. Ongoing trials with ezetimibe/statin over statin alone (88,89) or placebo (90,91) will further elucidate the occurrence of ezetimibe-associated side effects. Specifically, the ezetimibe and simvastatin in hypercholesterolaemia enhances atherosclerosis regression (ENHANCE) trial (88) seeks to compare combination treatment of ezetimibe with simvastatin (10/80 mg) vs. simvastatin (80 mg) alone (+ placebo) in reversing atherosclerosis of the carotid artery wall in patients with heterozygous FH (n = 725). The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study (90) aims at evaluating the effect of ezetimibe/simvastatin treatment in the disease burden reduction in patients with aortic stenosis (n = 1400). The Study of Heart And Renal Protection (SHARP) (91) will compare the LDL cholesterol lowering effect of combined ezetimibe/simvastatin treatment vs. placebo in chronic kidney disease patients (n = 9000). Finally, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) (89) has been designed to evaluate the risk reduction provided by ezetimibe/simvastatin (10/40 mg) vs. simvastatin (40 mg) alone in patients with acute coronary syndromes (n = 10,000). None of the aforementioned trials, however, has adverse effects as a primary endpoint.

All things considered, ezetimibe seems to be a reasonable alternative option for hyperlipidaemic patients intolerant to other lipid lowering drugs, as well as a beneficial supplementary agent for patients who do not reach the recommended LDL cholesterol levels with their current hypolipidaemic treatment. As is the case with all medications though, physicians should be alert to recognise unusual adverse effects, especially when ezetimibe is prescribed concomitantly with other drugs and report them to regulatory authorities.

References

1 American Heart Association. 1999 Heart and Stroke Statistical Update. Dallas: American Heart Association, 1999.

2 World Health Organization. World Health Report. Report of the Director-General. Geneva: WHO, 1998.

3 World Health Statistics 2007. http://www.who.int/statistics (accessed 29 May 2007).

4 Baigent C, Keech A, Kearney PM et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 15 randomised trials of statins. Lancet 2005; 366: 1267–78.

5 Knottsen DN, Filippatos TD, Mikhailidis DP et al. Statin-associated adverse effects beyond muscle and liver toxicity. Atherosclerosis 2006; Epub ahead of print.

6 Bays H. Ezetimibe. Expert Opin Investig Drugs 2002; 11: 1587–604.

7 Altman SW, Davis HR Jr, Zhu LJ et al. Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption. Science 2004; 303: 1201–4.

8 Davis HR Jr, Zhu LJ, Hoos LM et al. Niemann-Pick C1 Like 1 (NPC1L1) is the intestinal physiostero and cholesterol transporter and a key modulator of whole-body cholesterol homeostasis. J Biol Chem 2004; 279: 33586–92.

9 Sudhop T, Lutjohann D, Kodal A et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation 2002; 106: 1943–8.

10 Hildemann SK, Barho C, Karmann B et al. Dual cholesterol inhibition with ezetimibe/simvastatin in pre-treated hypercholesterolemic patients with coronary heart disease or diabetes mellitus: prospective observational cohort studies in clinical practice. Curr Med Res Opin 2007; 23: 713–9.

11 Blagden MD, Chipperfield R. Efficacy and safety of ezetimibe co-administered with atorvastatin in untreated patients with primary hypercholesterolaemia and coronary heart disease. Curr Med Res Opin 2007; 23: 767–75.

12 Kosoglu T, Meyer I, Velti EP et al. Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor ezetimibe and simvastatin. Br J Clin Pharmacol 2002; 54: 309–19.

13 Kosoglu T, Statkevich P, Fruchart JC et al. Pharmacodynamic and pharmacokinetic interaction between fenofibrate and ezetimibe. Curr Med Res Opin 2004; 20: 1197–207.

14 Kosoglu T, Statkevich P, Meyer I et al. Effects of ezetimibe on the pharmacodynamics and pharmacokinetics of lovastatin. Curr Med Res Opin 2004; 20: 955–65.

15 Kosoglu T, Statkevich P, Yang B et al. Pharmacodynamic interaction between ezetimibe and rosvastatin. Curr Med Res Opin 2004; 20: 1185–95.

16 Reyderman L, Kosoglu T, Cutler DL et al. The effect of fluvastatin on the pharmacokinetics and pharmacodynamics of ezetimibe. Curr Med Res Opin 2005; 21: 1171–9.

17 Moon YS, Chun P, Chung S. Ezetimibe and fenofibrate combination therapy for mixed hyperlipidemia. Drugs Today (Barc) 2007; 43: 35–45.

18 Jelssof NE, Ballantyne CM, Xydaikis AM et al. Effectiveness and tolerability of adding ezetimibe to niacin-based regimens for treatment of primary hyperlipidaemia. Endocr Pract 2006; 12: 159–64.

19 Rivers SM, Kane MP, Busch RS et al. Colesevelam hydrochloride–ezetimibe combination lipid-lowering therapy in patients with diabetes or metabolic syndrome and a history of statin intolerance. Endocr Pract 2007; 13: 11–6.

20 Farnier M, Roth E, Gil-Extremera B et al. Efficacy and safety of the coadministration of ezetimibe/simvastatin with fenofibrate in patients with mixed hyperlipidemia. Am Heart J 2007; 153: 335.e1–8.

21 McKenney JM, Farnier M, Lo KW et al. Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. J Am Coll Cardiol 2006; 47: 1584–7.

22 Daskalopoulou SS, Mikhailidis DP. Ezetimibe/simvastatin single tablet versus rosuvastatin in patients with hypercholesterolemia. Curr Med Res Opin 2006; 22: 2037–9.

23 Daskalopoulou SS, Mikhailidis DP. Reaching goal in hypercholesterolaemia: dual inhibition of cholesterol synthesis and
absorption with simvastatin plus ezetimibe. Curr Med Res Opin 2006; 22: 511–28.
24 Gazi IF, Mikhailidis DP. Non-low-density lipoprotein cholesterol-associated actions of ezetimibe: an overview. Expert Opin Ther Targets 2006; 10: 851–66.
25 Kalogirou M, Tsimhodimos V, Gazi I et al. Effect of ezetimibe monotherapy on the concentration of lipoprotein subfractions in patients with primary dyslipidemia. Curr Med Res Opin 2007; 23: 1169–78.
26 Mikhailidis DP, Wierzbicki AS, Daskalopoulos SS et al. The use of ezetimibe in achieving low density lipoprotein lowering goals in clinical practice: position statement of a United Kingdom consensus panel. Curr Med Res Opin 2005; 21: 959–69.
27 Ahmad I, Ruby E, Usman H et al. Ezetimibe-induced acute pancreatitis. South Med J 2007; 100: 409–10.
28 Fux R, Morike K, Gundel UF et al. Ezetimibe and statin-associated myopathy. Ann Intern Med 2004; 140: 671–2.
29 Phillips PS. Ezetimibe and statin-associated myopathy. Ann Intern Med 2004; 141: 649.
30 Simard C, Poirier P. Ezetimibe-associated myopathy in monotherapy and in combination with a 3-hydroxy-3-methylglutaryl coenzym e A reductase inhibitor. Can J Cardiol 2006; 22: 141–4.
31 Wefald LA, Flach LA. Myopathy associated with atorvastatin- ezetimibe combination therapy. Pharmacotherapy 2007; 27: 309–11.
32 Liu Q, Tobias H, Petrovic LM. Drug-induced liver injury associated with ezetimibe therapy. Drug Sci 2007; 52: 602–5.
33 Perez-Calvo J, Civirea-Murillo F, Caballo A. Worsening myopathy associated with ezetimibe in a patient with McArdle disease. Q J Med 2005; 98: 461–2.
34 Panichi V, Manca-Rizza G, Paoletti S et al. Safety and effects on the lipid and C-reactive protein plasma concentration of the association of ezetimibe plus atorvastatin in renal transplant patients treated by cyclosporine-A: a pilot study. Biomed Pharmacother 2006; 60: 249–52.
35 Purhonenparvu JL, Keough-Ryan T, Kiberd M et al. Treatment of hypercholesterolemia with ezetimibe in the kidney transplant population. Transplant Proc 2005; 37: 1033–5.
36 Kohenle M, Pieteruck F, Kribben A et al. Ezetimibe for the treatment of uncontrolled hypercholesterolemia in patients with high-dose statin therapy after renal transplantation. Am J Transplant 2006; 6: 205–8.
37 Buchanan C, Smith L, Corbett J et al. A retrospective analysis of ezetimibe treatment in renal transplant recipients. Am J Transplant 2006; 6: 770–4.
38 Fellstrom B. Impact and management of hyperlipidemia posttransplantation. Transplantation 2000; 70: S551–7.
39 Havranek JM, Wolfsen AR, Warnke GA et al. Monotherapy with ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia. Eur Heart J 2003; 24: 717–28.
40 Davidson MH, Garry T, Bettis R et al. Ezetimibe coadministration with simvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation 2003; 107: 2409–15.
41 Kelsey RB, Corbelli J, Sharp S et al. Efficacy and safety of ezetimibe coadministered with pravastatin in primary hypercholesterolemia. Am J Cardiol 2003; 91: 418–24.
42 Melani L, Mills R, Hassman D et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Eur Heart J 2003; 24: 1467–94.
43 Ballantyne CM, Houri J, Notarbartolo A et al. Effect of ezetimibe coadministered with atorvastatin in 62 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation 2003; 107: 2409–15.
44 Kelsey RB, Corbelli J, Sharp S et al. Efficacy and safety of ezetimibe coadministered with pravastatin in primary hypercholesterolemia. Am J Cardiol 2003; 91: 418–24.
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System associated hepatic apolipoprotein B overproduction and insulin resistance. *J Clin Invest* 1993; 92: 160–8.

Phillips PS, Ilaas RH, Bannykh S et al. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* 2002; 137: 581–5.

Phillips PS, Phillips CT, Sullivan MJ et al. Statin myotoxicity is associated with changes in the cardiopulmonary function. *Atherosclerosis* 2004; 177: 183–8.

Lebo RV, Gorin F, Fletterick RJ et al. High-resolution chromosome sorting and DNA blot analysis assign McArdle's syndrome to chromosome 11. *Science* 1984; 225: 57–9.

Jacobson TA, Armani A, McKenney JM et al. Safety considerations with gastrointestinal active lipid-lowering drugs. *Am J Cardiol* 2007; 99: 47C–55C.

Stolk MF, Bex MC, Kuypers KC et al. Severe hepatic side effects of ezetimibe. *Clin Gastroenterol Hepatol* 2006; 4: 908–11.

van Heyningen C. Drug-induced acute autoimmune hepatitis during combination therapy with atorvastatin and ezetimibe. *Ann Clin Biochem* 2005; 42: 402–4.

Obermayer-Straub P, Schaefer F, Sullivan MJ et al. Ezetimibe and steady-state cyclosporine in renal transplant patients. *Clin Pharmacol Ther* 2005; 78: 117–41.

Phillips PS, Haas RH, Bannykh S et al. Statin-associated myopathy coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation* 2002; 105: 2469–75.

Koshman SL, Lalonde LD, Burton I et al. Supratherapeutic response to ezetimibe administered with cyclosporine. *Ann Pharmacother* 2005; 39: 1561–5.

Bergman AL, Burke J, Larson P et al. Interaction of single-dose ezetimibe and steady-state cyclosporine in renal transplant patients. *J Clin Pharmacol* 2006; 46: 328–36.

Kosoglou T, Statkevich P, Johnson-Levonas AO et al. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2005; 44: 467–94.

Zetia [ezetimibe]. http://www.zetia.com (accessed 29 May 2007).

http://www.merck.com/newsroom/press_releases/product/2004_1109_enhance.html (accessed 1 June 2007).

Kastelein JJ, Sager PT, de Groot E et al. Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia. Design and rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial. *Am Heart J* 2005; 149: 234–9.

http://www.merck.com/newsroom/press_releases/product/2004_1109_enhance.html (accessed 1 June 2007).

Baigent C, Landry M. Study of Heart and Renal Protection (SHARP). *Kidney Int Suppl* 2003; 84: S207–10.