

Review

Role of Ezetimibe and Statins in Dyslipidemia Patients

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Abstract

Cardiovascular diseases are the leading cause of premature mortality globally. It is associated with significant morbidity and socioeconomic burden henceforth numerous initiatives have been taken to lower the risk in patients through preventive measures. The pathogenesis and progression of nearly all cardiovascular diseases are primarily caused by atherosclerosis and the association of cardiovascular disease risk to dyslipidemia is well-established since it increases the risk of cardiovascular events. Therefore, managing cholesterol, especially low-density lipoprotein, to reduce the burden of atherosclerotic plaque and, potentially, future cardiac complications, has been a key component of preventive measures. Due to its simplicity in dosage, lack of significant medication interactions, and favourable safety profile, statins have been the gold standard therapy for the treatment of dyslipidemia. However, the need for combined therapy arises when statin medication alone is insufficient to effectively reduce increased cholesterol levels. Ezetimibe is frequently added to regimens to support cholesterol reduction by preventing cholesterol absorption. Combinations of statin and ezetimibe may be a beneficial treatment choice for high-risk individuals who necessitate further lowering of cholesterol. Studies in the literature demonstrate that statin plus ezetimibe combined therapy is more beneficial and safer than high-intensity statin monotherapy, which implies that adding ezetimibe to statin should be favoured over increasing statin dose and that high-intensity statin is needed to be administered more carefully, especially in patients with related risks. The purpose of this research is to review the role of ezetimibe and statins in dyslipidemia patients.

Keywords: *cardiovascular, statin, ezetimibe, combination, dyslipidemia*

Introduction

The primary cause of early mortality and disability among individuals is cardiovascular disease (CVD), and its prevalence is rising around the globe. Due to their significant impact on the rising cost of healthcare, CVDs also place a significant socioeconomic burden on the general populace. The pathogenesis and progression of nearly all CVDs are primarily caused by atherosclerosis, which additionally causes peripheral vascular disease, coronary artery disease, cerebrovascular disease, venous thromboembolism, myocardial infarction, cardiac arrhythmias, and stroke (1). The association of CVD risk with dyslipidemia is well-established and is also strongly supported in the literature through findings from various clinical trials and long-term studies (2). Dyslipidemia is characterized by increased levels of triglycerides, low-density lipoprotein cholesterol (LDL-C), low levels of high-density lipoprotein cholesterol (HDL-C), and/or higher total cholesterol. Increased blood lipid levels, in particular, exacerbate the incidence of atherosclerosis. The development of arterial plaques and abnormal LDL-C levels complicate an elevated risk of CVD due to atherosclerosis (3).

The increased burden of CVD morbidity and mortality has led to the development and practice of various initiatives and strategies to decrease the risk among patients. Managing cholesterol, especially low-density lipoprotein, to reduce the burden of atherosclerotic plaque and, potentially, future cardiac events, has been a key component of prevention. Due to their simplicity in dosage, lack of significant medication interactions, and favourable safety profile, statins have been the gold standard therapy for the management of dyslipidemia. However, unfortunately, statin medication alone is not always sufficient to effectively reduce a patient's increased cholesterol levels, and combined therapy may be necessitated. Ezetimibe is frequently added to treatment regimens to support cholesterol reduction by preventing cholesterol absorption (4). Combinations of statins and ezetimibe may be a beneficial treatment choice for high-risk individuals who necessitate further lowering of LDL-C. By inhibiting both sources of

cholesterol, these combinations may be able to overcome some of the adverse effects of statin monotherapy (5).

Statins act by blocking HMG-CoA reductase, which is an essential enzyme in the production/synthesis of cholesterol (6). While ezetimibe acts as a Niemann-Pick C1-Like 1 inhibitor that functions by preventing cholesterol absorption at the small intestine's brush border (7). Statins are often well tolerated, although frequent reports of statin-associated muscular complaints have led to statin cessation. Other notable side effects of statin medication include abnormal liver enzymes. Furthermore, the increased chance of adverse effects with dosage increases is a noteworthy concern. Therefore, for patients who have risk factors for toxicities related to the liver or muscles, low-dose statin medication or a different treatment plan should be taken into consideration. Since high-intensity statin medication carries a higher risk than standard statin therapy, ezetimibe is a highly advised adjunct therapy when used with statins. Ezetimibe modestly lowers LDL-C by about 18% when used alone; however, combination therapy using ezetimibe and statins is predicted to have superior outcomes (8). The purpose of this research is to review the role of ezetimibe and statins in patients with dyslipidemia.

Methodology

This study is based on a comprehensive literature search conducted on August 31, 2023, in the PubMed, Web of Science, Science Direct, and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the role of ezetimibe and statins in patients with dyslipidemia. There were no restrictions on date, language, participant age, or type of publication.

Discussion

The risk of atherosclerotic CVD has been shown to be significantly decreased by statins. Although the necessity for statin combination therapy is prompted by unmet LDL-C objectives and atherosclerotic CVD risk reduction requirements, With the ability to reduce LDL-C by approximately 10%–18% and Apo B by 11%–16%, ezetimibe is a cholesterol-lowering medication from the class of cholesterol absorption inhibitors. When used in combination with statin therapy, an additional 25% decrease in LDL-C or a reduction in total LDL-C of 3%–61% is noted. Atherosclerotic CVD risk reduction translates into effects on LDL-C and other lipoprotein fractions. When combined with statin therapy, ezetimibe is one of the few hypolipemic drugs that further reduces the risk of atherosclerotic CVD. In addition to its hypolipemic action, current findings on ezetimibe support the existence of pleiotropic anti-inflammatory and antioxidant activities, which are accountable for this additional atherosclerotic CVD risk reduction over and above statin monotherapy. Patients who are unable to reach their desired LDL-C levels with statin monotherapy are prescribed ezetimibe in combination with a maximum or maximally tolerated statin therapy. In cases of statin-related muscle complaints, ezetimibe is used in conjunction with low-to-moderate statin dosage therapy or with second- or third-line statins. The combined therapy is mainly risk-free (9).

Evidence from literature

Studies comparing the atorvastatin-ezetimibe combination's effectiveness in lowering cholesterol with that of statin dose titration or switching to a more potent statin repeatedly demonstrated that the combination therapy offered greater LDL-C reduction, translating into a higher percentage of patients meeting their lipid goals. Combinations of simvastatin and ezetimibe have been demonstrated to cut the incidence of major atherosclerotic events in a number of clinical settings to a degree that appears comparable to that seen with statins for the same degree of absolute LDL-C lowering. Additionally, it has been demonstrated that

atorvastatin and ezetimibe taken together substantially more frequently than atorvastatin alone cause the regression of coronary atherosclerosis as evaluated by intravascular ultrasonography in patients. Combinations of atorvastatin and ezetimibe are often well tolerated. In certain trials with lengthy follow-up periods, prior concerns regarding the potential increase in the incidence of cancer with ezetimibe were ruled out (5). Findings of a study by Sakuma et al. reported that in coronary artery disease patients with poorly managed dyslipidemia, add-on ezetimibe medication appears superior to double-dose statin therapy in terms of lowering LDL-C levels, lipid peroxidation, and inflammation (10).

Vareka et al. demonstrated in their findings that in hyperlipidemia patients who had not reached the indicated target values for LDL-C, the inclusion of ezetimibe in a dose of 10 mg led to a subsequent considerable reduction in both total cholesterol and LDL-C. Additionally, it made it possible for more individuals to achieve the suggested plasma lipid concentrations. The procedure was risk-free and had no side effects (11). Similarly, results of a meta-analysis concluded that low- or moderate-intensity statin plus ezetimibe combined therapy is more beneficial and safer than high-intensity statin monotherapy, which implies that adding ezetimibe to statin should be preferred over increasing statin dose and that high-intensity statin needs to be administered more carefully, especially in patients with related risks (8). Findings from another meta-analysis also demonstrated that major adverse cardiovascular events and all-cause mortality were considerably reduced by statin and ezetimibe combination therapy (12).

Boutari et al. narrated that patients with hypercholesterolemia or dyslipidemia, with or without diabetes, and with or without CVD, can take rosuvastatin and ezetimibe together without experiencing any side effects. Compared to simvastatin/ezetimibe or rosuvastatin monotherapy, this medicine combination allowed a larger percentage of patients to meet approved LDL-C objectives without experiencing any significant side effects. Rosuvastatin/ezetimibe appears to be a

potent and generally well-tolerated medication combination suitable for the therapy of hypercholesterolemia and dyslipidemia in adults (13). Similarly, Le et al. reported that switching from statins to a combination of ezetimibe/simvastatin medication generally improved the lipoprotein subclass profile and Lp-PLA2 activity in diabetic patients with dyslipidemia more than statin dose-doubling and was comparable with rosuvastatin 10 mg, consistent with its lipid benefits (14). Results of a study by Shin and Choi showed that, compared to statin monotherapy, the combined therapy provided a much higher reduction in LDL-C. With combination therapy compared to statin monotherapy, a substantial improvement was seen in the levels of HDL-C, total cholesterol, triglycerides, and apolipoprotein B, but not apolipoprotein A1. Additionally, compared to statins alone, combination treatment dramatically decreased fasting blood glucose levels. There were no appreciable differences in treatment-related adverse events between the two therapies in terms of safety. In comparison to statin monotherapy, statin-ezetimibe combination therapy improves levels of LDL-C and other lipids without raising the risk of adverse effects (15).

Strilchuk et al. described that in many high-risk patients, the combined impact of ezetimibe and rosuvastatin makes it possible to achieve cholesterol targets while avoiding some of the safety concerns associated with high dosages of intensive statin therapy. Due to enhanced NPC1L1 gene expression, patients with diabetes appear to absorb cholesterol more efficiently than non-diabetic patients, providing extra benefits from ezetimibe. The triglyceride-lowering and anti-inflammatory properties of rosuvastatin are also enhanced by ezetimibe. The rosuvastatin/ezetimibe relationship is a beneficial option for statin dose up-titration due to its outstanding safety profile and lack of clinically significant drug-drug interactions (16). The fact that ezetimibe neither induces nor inhibits the cytochrome P450 system contributes to its favourable metabolic profile and low drug-drug interactions. It is mostly metabolised by the liver and eliminated in the faeces, and most people who

use it report no serious adverse effects. A significant reduction in LDL-C levels was produced by the combination of ezetimibe and statin therapy compared to doubling the dose of statin atorvastatin or simvastatin (17).

Ezetimibe and simvastatin combination therapy regularly decreases LDL-C more effectively than statin monotherapies, in accordance with a number of clinical research studies findings. Additionally, the combination therapy's safety and tolerability profiles appear to be comparable to those of low-dose statin monotherapies (18). Similarly, evidence from randomized controlled studies conducted on a number of individuals revealed that adding ezetimibe to statins, as opposed to increasing the statin dose, resulted in significantly more patients meeting their LDL-C goals and much fewer patients stopping their medication due to adverse effects (19). Likewise, Zhu et al. reported in their findings that ezetimibe and atorvastatin combination therapy significantly reduced LDL-C, non-HDL-C, total cholesterol, and triglycerides levels by 14.16%, 14.01%, 11.06%, and 5.96%, respectively, when compared to double-dose atorvastatin monotherapy ($p < 0.001$). There was no discernible difference between statin combination medication and monotherapy in the frequency of adverse events. Ezetimibe paired with atorvastatin has a strong therapeutic impact (20). Furthermore, Chauhan et al. concluded that simvastatin and ezetimibe combination therapy is superior to simvastatin monotherapy alone in terms of lowering LDL-C levels (21). Our review highlights the efficacy and safety of ezetimibe and statins in dyslipidemia, which is backed by sufficient evidence from clinical studies in the literature of recent times, which is the strength of the study. However, this combination of various strengths and dosages could not be compared and addressed in this paper since it is beyond the scope of our study and is a limitation of our study, although we aim to evaluate it in our subsequent research studies.

Conclusion

It is evident that using ezetimibe in conjunction with a statin is an effective way to lower LDL-C in

individuals at risk for or already suffering from CVD. It is also a worthwhile option for those who are unable to reach their desired LDL-C levels using the most tolerated statin potency. The combination is generally well tolerated and has a simple administration regime with minimal drug interactions. To further understand the advantages of this combination medication and its appropriate role in treatment, more research on clinical outcomes, such as the incidence of significant adverse cardiovascular events, is needed.

Disclosure

Conflict of interest

There is no conflict of interest

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Ethical consideration

Non applicable

Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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