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DRUG PROFILE

Rosuvastatin and ezetimibe for the treatment of dyslipidemia and hypercholesterolemia

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ABSTRACT

Introduction: Statins are powerful lipid-lowering agents which reduce cardiovascular (CV)–related morbidity and mortality. However, a large proportion of patients cannot attain the target low-density lipoprotein cholesterol (LDL-C) levels, despite receiving maximally tolerated doses of high-intensity statins. Also, adherence to treatment may be reduced due to statin-induced myopathy or other side effects. For these reasons, guidelines recommend adding the cholesterol absorption inhibitor ezetimibe.

Areas covered: Authors discuss the main pharmacological characteristics of rosuvastatin and ezetimibe, their lipid-lowering and pleiotropic effects, as well as the clinical effects of the fixed dose combination of these drugs when used to treat dyslipidemia.

Expert opinion: The rosuvastatin/ezetimibe combination is safe and effective in patients with hypercholesterolemia or dyslipidemia with or without diabetes and with or without cardiovascular disease. This drug combination enabled higher proportions of patients to achieve recommended LDL-C goals than rosuvastatin monotherapy or the simvastatin/ezetimibe combination, without additional adverse events. Despite the lack of additional CV outcomes data and comparisons with atorvastatin/ezetimibe, rosuvastatin/ezetimibe appears as a potent and generally well-tolerated drug combination eligible for the management of hypercholesterolemia and dyslipidemia in adults. Recently, the 40 mg rosuvastatin/10 mg ezetimibe fixed combination was approved and is also evaluated.

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1. Introduction

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are the first line and the most prescribed lipid-lowering agents currently available; they remain the cornerstone for the treatment of hypercholesterolemia. Statins reduce cardiovascular (CV)–related morbidity and mortality and exert anti-inflammatory effects [1]. However, a large proportion of statin users cannot attain target low-density lipoprotein cholesterol (LDL-C) levels, despite the fact that they receive maximally tolerated doses. Also, adherence to treatment may be reduced due to statin-induced myopathy or other side effects [2].

Ezetimibe, an inhibitor of intestinal cholesterol absorption, combined with a statin provides a complementary option to lower LDL-C levels. Thus, while doubling the dose of statin or switching to another statin results in an additional reduction in LDL-C level of 6–8%, the addition of ezetimibe to statin therapy may further reduce LDL-C by 15–20% or more [3–5]. The most recent Guidelines of the European Society of Cardiology and European Atherosclerosis Society for the management of dyslipidaemias and the Guidelines of American College of Cardiology and American Heart Association Task Force on the Management of blood cholesterol [6,7], recommend adding ezetimibe to maximally tolerated statin treatment for patients who cannot achieve their LDL-C targets using statin monotherapy. Besides, ezetimibe allows the use of lower statin dosages and does not increase the risk for new-onset diabetes mellitus (NOD); it may even decrease the risk of NOD [8,9]. In a meta-analysis of randomized controlled trials (RCT), including 4344 participants, from 24 studies initially selected, 20 were finally included [10]. The statin/ezetimibe combinations induced substantial reductions in LDL-C, total cholesterol (TC), and triglycerides (TGs), but had minimal effects on high-density lipoprotein cholesterol (HDL-C) [10]. In another meta-analysis of five RCTs involving a total of 5080 patients, the changes recorded were as follows: −23.6% for LDL-C ($p < 0.0001$) and −10.7% for triglycerides (TGs) with an increase of 1.7% for high-density lipoprotein cholesterol (HDL-C) levels ($p < 0.0001$) [11]. In a systemic review, the differences were ezetimibe/statin vs statin monotherapy −14.1%, $p < 0.001$) [11]. Reduction in LDL-C levels attributed to adding ezetimibe to a statin was significantly greater than that induced by statin −15.3%, $p < 0.001$) [12]. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), that included 18,144 patients who had an acute coronary syndrome (ACS) during the last 10 days and an LDL-C from 50 to 100 mg/dl, evaluated the effect of ezetimibe combined with simvastatin, and compared it with that of simvastatin alone [13]. The simvastatin/ezetimibe combination substantially reduced the LDL-C levels and improved cardiovascular (CV) outcomes in comparison to simvastatin monotherapy [13].

Rosuvastatin is the most powerful available statin with greater results in decreasing LDL-C levels than with other statins and a comparable tolerability profile [14–16]. The fixed dose combination (FDC) of rosuvastatin/ezetimibe can

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Article highlights

- Rosuvastatin lowers plasma LDL-C levels by inhibiting HMG-CoA reductase activity.
- Ezetimibe lowers plasma LDL-C levels by inhibiting the absorption of cholesterol from the small intestine.
- The combination of the 2 drugs act in an additive way.
- The fixed combination of the two drugs is more effective than each drug administered as monotherapy.
- The fixed dose combination (FDC) of the 2 drugs is safe and cost-effective.
- Studies are needed to verify the expected reduction in cardiovascular events with this FDC.

be administered as an addition to diet and exercise for the management of hypercholesterolemia.

The position of the rosuvastatin/ezetimibe drug combination in the therapeutic armamentarium is very high. It is the last measure to take in order to treat dyslipidaemias before the use of PCSK9i. The replacement of the ezetimibe step if the LDL-C target is not achieved, by PCSK9i is not considered because for several reasons (ezetimibe is a pill orally taken, is cheaper, and does not reduce LDL-C to uncharted low LDL-C levels).

Given that our Outpatient Clinic is a Reference Center for familial hypercholesterolemia or other hypercholesterolemias with very high baseline LDL-C, covering half the country, we focused in this review on the effect of FDC rosuvastatin/ezetimibe on hypercholesterolemia rather than other dyslipidaemias, such as mixed dyslipidaemia. Our Outpatient Clinic data suggest that 70% of patients with heterozygous familial hypercholesterolemia attain the prespecified LDL-C target. In these patients there is no need to use the statin PCSK9i (which is more expensive). In the case that the target is not achieved we add a PCSK9i to the FDC. In this way we treat nearly all our patients, except for totally statin intolerant patients in which we use the ezetimibe plus PCSK9i combination.

This review discusses the efficacy and tolerability of rosuvastatin/ezetimibe combination in the treatment of dyslipidaemia and hypercholesterolemia.

2. Overview of the market and introduction to the drug

The pharmacological properties of rosuvastatin and ezetimibe [13,17,18] have been previously thoroughly documented. Rosuvastatin is a hydrophilic and hepatoselective potent HMG-CoA reductase inhibitor which lowers LDL-C by 46–55% and triglycerides (TG) levels by 15–31% and increases high-density lipoprotein cholesterol (HDL-C) by 6.1% [15–17]. In parallel it exerts pleiotropic effects, like anti-inflammatory, antioxidant, antithrombotic and endothelial protection [18–20]. Since only ~10% of rosuvastatin is metabolized by cytochrome P450 (CYP) 2C9 and its unmetabolized part is being excreted into the feces with the bile from the liver, there is low likelihood of drug–drug interactions [20–22]. Moreover, rosuvastatin may be linked with low rates of severe myopathy, rhabdomyolysis, and renal failure [23].

Ezetimibe is a potent cholesterol absorption inhibitor which binds to protein and not Niemann-Pick C1-like (NPC1L1) protein to selectively inhibit absorption of biliary and dietary cholesterol from small intestine [24]. It can be administered as monotherapy or in combination with a statin, at any time of the day [25,26]. Since also ezetimibe is not metabolized by CYP, it has insignificant drug–drug interactions [26].

The co-administration of rosuvastatin and ezetimibe does not seem to lead to any important pharmacokinetic interactions in healthy adults. Moreover, the fixed dose combination (FDC) of rosuvastatin/ezetimibe is bioequivalent, regardless of food intake, to the co-administration of the relevant doses of rosuvastatin and ezetimibe administered as individual tablets [27–29].

3. Clinical efficacy

Several studies have demonstrated the additive effects of ezetimibe/statin combination on the lowering of LDL-C and TG levels [26–28].

The Ildong Rosuvastatin & Ezetimibe for Hypercholesterolemia (IROSETTE) trial compared various doses of the combination of rosuvastatin/ezetimibe (5/10 mg, 10/10 mg, 20/10 mg) and rosuvastatin monotherapy (5, 10, 20 mg) in 396 patients with statin intolerance or insufficiency [30]. The decrease of mean LDL-C from the baseline for the total rosuvastatin/ezetimibe group was 57% and 44% for the total rosuvastatin group ($p < 0.05$), while 92% of combination group and 80% of rosuvastatin group reached the LDL-C goal after 8 weeks of treatment [30]. The safety and tolerability of ezetimibe/rosuvastatin FDC were similar with rosuvastatin monotherapy [30].

The Multicenter Randomized Study of Rosuvastatin and Ezetimibe (MRS-ROZE) [31] examined the efficacy of rosuvastatin/ezetimibe combination (5, 10, or 20 mg/day) and 10 mg/day of rosuvastatin alone in 407 patients with primary hypercholesterolemia for 8 weeks [31]. The FDC provided significantly greater LDL-C by 56%-63%, total cholesterol (TC) by 37%-43%, and TGs by 19%-24% [31]. These reductions were significantly superior than those achieved by rosuvastatin monotherapy [31]. Also, these reductions were more prominent in diabetes mellitus (DM) and metabolic syndrome (MetS) patients [31].

A 12-week randomized, placebo-controlled, multicenter study evaluated the efficacy of the combination therapy in Korean patients with high CV risk [32]. The mean LDL-C target achievement rate was 73% in the monotherapy group and 91% in the combination groups ($p = 0.01$ for the pooled groups) [32]. There was no significant difference between the 2 groups concerning the proportions of patients with adverse events [32].

Furthermore, the up-titration of rosuvastatin dose is not as effective as ezetimibe addition is [33]. The Efficacy and Safety of Ezetimibe Added On to Rosuvastatin Versus Uptitration of Rosuvastatin in Hypercholesterolemic Patients at Risk for Coronary Heart Disease (ACTE study), a 6 week study, compared ezetimibe added to stable rosuvastatin therapy *vs* up-titration of rosuvastatin from 5 to 10 mg or from 10 to 20 mg in 440 subjects at moderately high/high risk [33]. Pooled

results revealed that the addition of ezetimibe to rosuvastatin 5 or 10 mg decreased LDL-C levels by 21%, while up-titration of rosuvastatin to 10 or 20 mg decreased LDL-C levels by 6% ($p = 0.4$) [33]. Moreover, in another study with mixed hyperlipidemia ezetimibe helps rosuvastatin in TG-lowering and in its anti-inflammatory effects, also [34]. In patients with type 2 diabetes mellitus T2DM ezetimibe is more effective in LDL-C reduction because NPC1L1 expression is upregulated in diabetes gene expression, a critical mediator of cholesterol absorption [34].

In the a group of 1197 patients at risk of CVD that could not attain the LDL-C guideline target with monotherapy were included in the EXamination of Potential Lipidmodifying effects Of Rosuvastatin in combination with Ezetimibe versus Rosuvastatin alone (EXPLORER) study [35]. From these patients 469 were randomly assigned to either rosuvastatin 40 mg/day (n = 230) and the rest 239 to rosuvastatin 40 mg/ezetimibe 10 mg combination [35]. Substantially more patients on rosuvastatin/ezetimibe than rosuvastatin monotherapy attained their LDL-C goal (<100 mg/dl, 94.0% vs 79.1%, $p < 0.001$) and the LDL-C cholesterol goal (<70 mg/dl) for high-risk patients (79.6% vs 35.0%, $p < 0.001$) [35]. This was verified in an 8 week study in Korea, and eastern population [36].

The chromatographic technique described does not guarantee the stability of the individual components of the fixed drug combination, but is a relatively easy assay to confirm that stability has been maintained [37].

In a study (n = 89) patients with T2DM, FDC achieved in 12 weeks quantitative but also qualitative improvement of serum lipid levels in T2DM patients, suggesting that this combination could suppress the progression of atherosclerosis [38].

Since Human Immunodeficiency Virus (**HIV**) disease is associated with hyperlipidemia, due to the Highly Active AntiretRoviral Therapy (**HAART**) and possibly the disease itself, it often coexists with CVD [39,40]. The investigators, who examined the effect of ezetimibe addition to maximally tolerated statin treatment in 33 HIV patients who did not manage to achieve the LDL-C targets, showed that the addition of ezetimibe resulted in a beneficial effect on their lipidemic profile. The patients on drug combination reached 80% of LDL-C target, which was the intension of the study [40]. Mean total cholesterol was reduced by 32%, mean LDL-C by 45%, and mean TG by 49%, $p < 0.001$ for all [41]. This was verified by another study also [42].

Also, a study (Gauging the Lipid Effects of Rosuvastatin Plus Ezetimibe Versus Simvastatin Plus Ezetimibe Therapy [GRAVITY]) in 833 patients with CHD or CHD risk equivalent compared the efficacy and safety of co-administration of rosuvastatin 10 or 20 mg and ezetimibe with that of simvastatin 40 or 80 mg and ezetimibe [43]. The authors concluded that a significantly greater percentage of patients could reach the LDL-C target with the combination therapy of rosuvastatin/ezetimibe (96 *vs* 77%, respectively) than those who received simvastatin/ezetimibe (87% or 89% and 55% or 68% in the different dosage groups, respectively, $p < 0.01$) [43].

Beyond the beneficial effects of rosuvastatin/ezetimibe on the components of the lipid profile, it also contributes to the atherosclerotic plaque burden reduction. A study of 51 subjects with stable coronary artery disease requiring percutaneous coronary intervention found that the plaque volume decrease, assessed with serial volumetric intravascular ultrasound (IVUS) analysis, was greater in patients receiving the combination treatment than the monotherapy [44].

Interestingly, in a pilot study of 262 patients the rosuvastatin therapy intensified by ezetimibe decreased not only the LDL-C levels but also the major CV events that occurred during 12 months after vascular surgery when compared with rosuvastatin alone [45].

FDC included, in a crossover randomized study, 200 patients with mixed hyperlipidemia a beneficial change in TC, high-DL-C (HDL), TGs, small-dense LDL particles, lipoprotein(a) [Lp(a)], glucose, glycated hemoglobin, high-sensitivity C-reactive protein (hsCRP) in 12 weeks [46]. Besides, the pharmacokinetics of rosuvastatin are not dependent on time of dosing. Morning or evening administration is equally effective in lowering LDL-C". In this study half the patients received 10 mg/d of rosuvastatin in the morning and the other half in the evening. In the middle of the study the patients received the alternative time of regimen administration. Both times rosuvastatin had the same LDL-C lowering potential [46].

4. Safety and tolerability

Rosuvastatin and ezetimibe are generally well tolerated either as monotherapies or as combination therapy, when administered separately or as a FDC [30–33,36,43]. There was no significant difference between the overall incidence of adverse events between the rosuvastatin/ezetimibe groups and the rosuvastatin monotherapy groups in any trial. Moreover, the types of adverse events occurred in the 2 groups were in general similar [30–32]. The most common adverse events with rosuvastatin/ezetimibe were gastrointestinal, musculoskeletal and there were no significant differences between rosuvastatin/ezetimibe and rosuvastatin monotherapy recipients [30,32]. Regarding the transaminase and creatine kinase elevations (3 x ULN and 5 x ULN, respectively), they were rare and no significantly difference was noted between the two groups [30–32].

5. Regulatory affairs

The rosuvastatin/ezetimibe FDCs 5/10 mg, 10/10 mg, 20/10, and 40/10 mg have been approved both by Food and Drug Administration and European Medicines Agency (https://www.galinos.gr/web/drugs/main/companies/sanofi). This FDC is indicated as an adjunctive therapy to lipid-lowering diet and exercise for the management of primary hypercholesterolemia in adults. The 40/10 mg FDC is very useful for the treatment of heterozygous familial hypercholesterolemia [42]. After this dose the patient should use proprotein convertase subtilisin/kexin type 9

(PCSK9) inhibitors. The combination can be administered once daily, at any time of the day [43].

6. Cost effectiveness

The combination of rosuvastatin with ezetimibe is cost effective regarding lowering LDL-C levels [47]. The fixed combination of the 2 drugs (5/10, 10/10, 20/10, 40/10) has a mean cost in Europe from 20 to 25 €/month (from generic drugs from high impact international company) for up to 75% fall in LDL-C, and a significant reduction in TGs [47]. This is better than any other hypolipidaemic drug treatment for achieving the LDL-C therapeutic goal in patients at high risk for CV [47]. The cost effectiveness of the fixed rosuvastatin/ezetimibe combination was proved by reference [34]. The price looks very low, given that many expect that treatment with the FDC to cost more than 500 €/month. On the other hand, in our Country the combination of a powerful statin plus a PCSK9i costs lower that € 500 per month, 20 € for the statin and 350 € (175 x 2) for the PCSK9i injection. The later is payed totally by the state.

7. Conclusion

The rosuvastatin/ezetimibe combination seems to be an effective, potent and safe lipid-lowering option, able to significantly decrease LDL-C and TG levels and possibly CV risk [44,48,49]. Another benefit of the FDC may be the nonalcoholic fatty liver disease [49]. These benefits of rosuvastatin/ezetimibe *vs* rosuvastatin alone have also been observed in primary or mixed dyslipidemia, across key subgroups, like patients with diabetes mellitus or HIV. Furthermore, this drug combination is associated with a low risk of pharmacological interactions or clinically significant adverse events.

8. Expert opinion

The rosuvastatin/ezetimibe combination has an additive lipid-lowering effect and contributes to LDL-C target achievement, avoiding the safety issues associated with intensive statin therapy. Also, the substantial LDL-lowering effect is expected to significantly reduce CV risk. The normalization of lipid profile was reported in patients with hypercholesterolemia or dyslipidemia with or without diabetes, with or without cardiovascular disease. Given the good safety profile of ezetimibe, it may be a useful alternative option instead of statin dose uptitration, in patients who cannot tolerate any statin or high doses of statins. Moreover, the lack of pharmacological interactions for rosuvastatin make the rosuvastatin/ezetimibe combination a very competitive treatment, especially for the patients with polypharmacy [50]. Additionally, the FDC of the 2 drugs, which can be administered orally once daily, at any time of the day, in a single tablet should improve patient adherence to the treatment. All these advantages make the specific drug combination much more efficient and provide an advantage over simvastatin/ezetimibe, since simvastatin is less powerful than rosuvastatin, ideally needs to be administered in the evening, and is associated with several drug-drug interactions [50].

Nevertheless, there is a need for large, prospective, randomized, controlled studies evaluating the long-term effects of rosuvastatin/ezetimibe combination in relation to the CV events or the parameters associated with the CV risk, such as atherosclerotic plaque volume, flow-mediated dilation, pulse wave velocity. Also, trials comparing the efficacy of rosuvastatin/ezetimibe with that of atorvastatin/ezetimibe would be useful and interesting to better define the value and the position of rosuvastatin/ezetimibe in the treatment of hypercholesterolemia. However, we need to consider that such trials are unlikely to become available since the drugs concerned are now available as generic formulations.

The addition of ezetimibe to a statin the authors should stress that the access to ezetimibe is restricted in some countries, and in few countries prescription of ezetimibe is still limited only to selected specialists [9]. This should change if we intent to attain LDL-C goals in a large part of the high risk or statin intolerant or both population [9].

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Declaration of interest

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