

Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular risk patients:

BACKGROUND:

- Among the therapies currently approved for lowering lipoprotein cholesterol (LDL-C), statins are the most commonly prescribed and have shown the greatest ability to lower LDL-C and reduce coronary heart disease.
- Despite the availability of statins and other lipid lowering therapy, even when they are used in combination, many high-risk patients do not reach target LDL-C levels.

OBJECTIVE:

- To compare lipid-lowering efficacy of adding alirocumab to rosuvastatin versus other treatment strategies

METHODS

- **Design:** Multicenter, double-blind, double dummy, randomized parallel trial
- **Duration:** treatment for 24 weeks, follow up at 32 weeks
- **Inclusion criteria:** Adult patients with hypercholesterolemia at very-high or high CV risk receiving rosuvastatin 10 or 20 mg/day for at least 4 weeks prior to screening. Very-high CV risk patients with a history of coronary heart disease (CHD), non-CHD CV disease, or diabetes mellitus with target organ damage were included if LDL-C was >70 mg/dL at screening. High-risk CV patients without documented CHD or CVD but with a 10-year risk >5%, moderate chronic kidney disease, or diabetes with no target organ damage, were included if LDL-C was >100 mg/dL
- **Exclusion criteria:** Patients already taking ezetimibe, or taking statins other than rosuvastatin
- **Primary outcome measure:** Percent change from baseline in calculated LDL-C value at week 24
- **Secondary outcome measures:** Difference in calculated LDL at week 12, non-HDL, Apo B, lipoprotein a, fasting triglycerides, and HDL at week 24.
- A total of 305 patients were randomized to one of the six treatment groups
 - 49 received alirocumab and 10 mg rosuvastatin
 - 48 received ezetimibe and 10 mg rosuvastatin
 - 48 doubled dose to 20 mg rosuvastatin
 - 54 received alirocumab and 20 mg rosuvastatin
 - 53 received ezetimibe and 20 mg rosuvastatin
 - 53 doubled dose to 40 mg rosuvastatin
- Alirocumab was initially dosed at 75 mg subcutaneously every 2 weeks, and randomly increased at week 12 to 150 mg every 2 weeks
- Ezetimibe was dosed at 10 mg once daily
- A total sample size of 300 patients was determined to provide 90% power. This included 50 patients in each treatment group.

- Data handling method was intent-to-treat

RESULTS

- 18 participants discontinued treatment early due to adverse events
- In the 10 mg baseline group, add-on alirocumab reduced LDL-C by 50.6%, add on ezetimibe reduced LDL-C by 14.4%, and double dose (20 mg) rosuvastatin reduced by 16.3%.
- In the 20 mg baseline group, add-on alirocumab had a 36.3% reduction, 11% for the add-on ezetimibe group and 15.9% for doubling the dose to 40 mg.
- **Author's conclusion:** Patients with hypercholesterolemia at high or very-high CV risk, alirocumab provided clinically important and incremental reductions in LDL-C compared with the currently available options. Both alirocumab 75 and 150 mg are well tolerate, allowing a treat-to-target approach in patients not at their LDL-C goal.

STRENGTHS

- Multi-center
- Used intent-to-treat data handling methods

LIMITATIONS

- Not all lipid lowering therapy was excluded
- Patients lifestyle was not assessed
- Small sample size in treatment groups
- Non-study medications taken by patients were not reported

CONCLUSION

- Although the study showed alirocumab treatment caused a significant decrease in LDL-C values, the long-term adverse effects or affect on mortality has not been determined. Statins have shown to have a mortality benefit even though they do not lower the LDL cholesterol as significantly as alirocumab.
- Currently, alirocumab costs about \$1,200 per month supply. Since not much data is available the possible mortality benefit of alirocumab, high intensity statins will continue to be used for high-risk patients. Rosuvastatin is currently around \$300 per month, while atorvastatin is even cheaper at around \$100 per month depending on the manufacturer.
- Further research:
 - A trial should include diet and exercise factors in the study participants
 - Long-term side effects and if there is a mortality benefit need to be evaluated to further research alirocumab safety and place in therapy

Reference: Farnier M, Jones P, Serverance R, Averna M, Steinhagen-Thiessen E, Colhoun et al. (2015) Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular risk patients: the ODYSSEY OPTIONS II randomized trial. *Atherosclerosis*. 2015 July 17;244:138-146.

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