Title: LIBerate-HeFH: Novel PCSK9-Inhibitor in Heterozygous Familial Hypercholesterolemia
Participants: Dr Frederik Raal
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Dr Frederick Raal

"So I'm Derek Raal. I'm an endocrinologist based in Johannesburg in South Africa, and my interest has been novel treatments of familial hypercholesterolemia.

Unmet Needs in Patients with Heterozygous Familial Hypercholesterolemia

Well, patients with familial hypercholesterolemia have very markedly elevated LDL cholesterol levels, as you know from birth. Standard therapy is high-intensity statins together with ezetimibe plus agents, but we can't get the vast majority of patients to a decent LDL cholesterol level, so we need newer therapies and a very exciting group. Therapies are the PCSK9 inhibitors.

Mechanism of Action of LIB003 and Other PCSK9 Inhibitors Comparison

The standard PCSK9 inhibitors are monoclonal antibodies. But I'm talking about there's a new generation, which is a small binding protein called LIB003, or lerodalcibep, which the advantage of this, it's a much smaller protein, so it can be given in a smaller volume, it's stable at room temperature, and it can be administered less frequently than monoclonal antibodies, which normally have to be administered every two weeks. This therapy is administered just once a month.

Study Design and Baseline Patient Characteristics

So I'm presenting the results of this called the LIBERATE Heterozygous FH study, which was a study in patients with heterozygous familial hypercholesterolemia that still had elevated LDL cholesterol levels despite treatment with high-intensity statins. Plus ezetimibe because that's an unmet need. And the study design, we planned to enroll about 500 patients, we enrolled 478 and they were randomized two to one, either to

lerodalcibep or placebo. It was a 24-week study, and the primary endpoint was the LDL reduction at week 24.

Key Results

So the key results with this therapy, the placebo-corrected reduction in LDL cholesterol was about 60%, which is remarkable, that's an absolute reduction in LDL cholesterol of over two millimoles. And importantly, it allowed about 70% of the patients to achieve the ESC recommended target. So that's a 50% reduction in LDL cholesterol, which was achieved in 80%. And also the LDL targets of 1.4 millimoles per lead in those with established cardiovascular disease or 1.8 in those without. In about 70% of patients, there was also reduction in EPO B of about 45% and lipoprotein little A was reduced by about 25%. So it's in keeping, in fact, the results are even better than what we've seen with the monoclonal antibodies.

Safety Events

Well, safety events with all injectables, there was no difference between the standard safety events between placebo and the study drug, but there was an increased incidence of injection site reactions. But these were all mild or moderate, none were severe, none were persistent. So overall there was about a 3% incidence of injection site reactions. But you're giving an injection once a month, so a small little injection site reaction is of no concern.

Potential Impact

Well, it's going to add another new drug to the armamentarium for the treatment of these very difficult to treat patients. The advantages of this therapy is that it's a smaller volume and it's given less frequently only once a month, and it's going to get the vast majority of patients to LDL cholesterol target.

Next Steps

We tried the drug first in the most deserving patients, so those are with familial hypercholesterolemia, both heterozygous and homozygous. Familial hypercholesterolemia. But naturally the greater use would be in patients with established atherosclerotic cardiovascular disease or at high risk for cardiovascular disease, though those studies are actually ongoing and they're going to be ending in November this year, and we will see look forward to seeing the results. Much larger studies in patients at high risk."