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Cystic Fibrosis Research News

Title:

Lumacaftor/ivacaftor improves liver cholesterol metabolism but does not influence hypocholesterolemia in patients with cystic fibrosis

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What was your research question?

The drug lumacaftor/ivacaftor has become available for patients with cystic fibrosis, homozygous for the deltaF508 mutation and older than 6 years, because it improves respiratory function.
Our research question was to determine if this drug also has positive effects on hepatobiliary function, intestinal absorption and liver metabolism of cholesterol and non-cholesterol sterols. The latter's are lipids like the precursors of cholesterol and plant sterols such as campesterol and sitosterol.

Why is this important?

Pancreatic insufficiency (PI) affects about 85% of patients with cystic fibrosis (CF). It causes poor intestinal absorption of nutrients such as lipids, proteins, and vitamins with important consequences for metabolism and the general health of patients.
By studying the metabolism and absorption of cholesterol, and non-cholesterol sterols, in patients with CF and PI, we found reduced intestinal absorption and increased liver synthesis of cholesterol and lower plasma cholesterol levels than healthy subjects.
According to Gail Martin's exhortation "Pass the butter ...", hypocholesterolemia (low levels of cholesterol) can be as harmful as hypercholesterolemia (high levels of cholesterol), therefore it should be corrected in these patients (Science Vol. 274, 11 October 1996)

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What did you do?

In this study, we evaluated the effects of treatment with lumacaftor/ivacaftor on cholesterol metabolism, intestinal lipid absorption and hepatobiliary function in 20 adult patients with CF homozygous for deltaF508. Before treatment, these patients had lower plasma cholesterol and vitamin E levels compared to those found in the control group (20 CF patients with PI and compound heterozygous for deltaF508 and another severe mutation).

What did you find?

The treatment of patients with lumacaftor/ivacaftor, after a period of 15 ± 6 months, showed normalization of liver synthesis of cholesterol comparable to that observed in healthy subjects. Moreover, the effect of the drug increased the intestinal lipid absorption and the levels of vitamin E, which correlated with the period of treatment with lumacaftor/ivacaftor. The drugs did not affect hypocholesterolemia, which slightly decreased after the treatment. Among the serum markers of liver damage/function, we found increased levels of an enzyme called alkaline phosphatase at the start of the study, which significantly decreased, on average by 38%, after the period of treatment.

What does this mean and reasons for caution?

Although this is a preliminary study, it suggests that lumacaftor/ivacaftor, affecting the CFTR protein, may improve the sterol transport between the intracellular and extracellular compartments through mechanisms not yet known, but with positive effects both on intestinal cells (improvement of absorption) and on liver cells (reduction in synthesis and/or increase in excretion of sterols). However, these effects are unable to correct the low levels of plasma cholesterol observed in most patients with CF. The "Hypocholesterolemia" is a marker of poor health and could expose the patients to an increased risk of depression, cancer, and other ill.

What's next?

To study how to increase plasma levels of cholesterol in these patients by using enzyme supplementation, personalizing the diet, as well by using new drugs. To study the relationship between the CFTR protein and the molecular mechanisms that regulate sterol transport between the intracellular and extracellular compartments.

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