European Cystic Fibrosis Society

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Cystic Fibrosis Research News

Title:
Lumacaftor-ivacaftor effects on cystic fibrosis-related liver involvement in adolescents with homozygous F508 del-CFTR

Lay Title:
Orkambi may improve liver disease in people with CF

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What was your research question?

Very few data have been reported documenting the effects on liver disease in people with CF using CFTR modulators. This is probably because people with CF and severe liver disease are not included in CFTR modulator trials. The objective of the study was to describe the effect of lumacaftor-ivacaftor treatment in a group of adolescents with two F508del mutations on features of involvement of liver disease in CF.

Why is this important?

Liver disease is the third cause of death after lung failure and transplantation-related complications in people with CF. No therapy (including ursodeoxycholic acid) has proven effective to prevent or halt the progression of liver disease towards structural changes of the liver (cirrhosis) and high pressure in the blood vessels of the liver (portal hypertension). We asked the question whether CFTR modulators might impact positively on the liver function. There has been no study reported to date, focusing on the evolution of liver outcomes in patients treated by lumacaftor-ivacaftor therapy.

What did you do?

We evaluated at the start of the treatment and at 12 months post therapy, clinical characteristics, liver blood tests, echo of the belly called ultrasound sonography (US), and the amount of fat in the pancreas and in the liver, an indirect measurement of liver disease. Signals (biomarkers) of CFTR activity (sweat chloride test, measurement of the cell function in the nose (nasal potential difference), and in the rectum (intestinal current measurement) were assessed at start and at 6 months therapy.

What did you find?

Of the 37 patients who started ivacaftor/lumacaftor treatment, 28 had enough measurements for analysis. Four patients were diagnosed with severe liver disease , 19 with other forms of CF liver involvement, and 5 with no signs of liver involvement. No negative (adverse) reactions on the functioning of the liver were documented. Blood tests of liver function, improved significantly following the start of lumacaftor-ivacaftor, and remained so after 12 months treatment, including the level of an important enzyme of the liver called GGT. Improvement in blood tests were more frequently found in the patients with the most worse functioning of the liver. This was not related with changes in liver and pancreas US and fat, and in the level of an enzyme resembling the function of the pancreas in the stools (fecal elastase), or lumacaftor-ivacaftor blood levels. The patients with the best improvement showed an important increase in biomarkers of CFTR activity.

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What does this mean and reasons for caution?

We predict that the improvement in the blood liver test with lumacaftor-ivacaftor therapy results, at least partially, from correction of the some liver malfunctioning due to the CFTR mutation. This result also raises the question whether lumacaftor-ivacaftor might prevent liver disease later in life. But as this study is only in a small sample of patients we must be cautious.

What's next?

These results are suggestive of a potential beneficial effect of CFTR modulators on CF liver disease and larger future studies are warranted to confirm these findings and evaluate if CFTR modulators can indeed improve the course of CF liver disease.

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