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Cystic Fibrosis Research News

Title:

Lumacaftor/Ivacaftor Therapy Fails to Increase Insulin Secretion in F508del/F508del CF Patients

Authors:

Amir Moheet[a], Daniel Beisang[b], Lin Zhang[c], Scott D. Sagel[d], Jill M. VanDalfsen[e], Sonya L. Heltshe[e,f], Carla Frederick[g], Michelle Mann[h], Nicholas Antos[i], Joanne Billings[a], Steven M. Rowe[j], Antoinette Moran[b] on behalf of the PROSPECT Investigators of the Cystic Fibrosis Foundation Therapeutics Development Network.

Affiliations:

[a]Department of Medicine, University of Minnesota, Minneapolis, MN
[b]Department of Pediatrics, University of Minnesota, Minneapolis, MN
[c]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN
[d]Department of Pediatrics, Children's Hospital Colorado and University of Colorado Anshutz Medical Campus, Aurora, CO
[e]Cystic Fibrosis Foundation Therapeutics Development Network Coordinating Center, Seattle, Children's Research, Seattle, WA
[f]Department of Pediatrics, University of Washington School of Medicine, Seattle, WA
[g]Jacobs School of Medicine and Biomedical Sciences of the University at Buffalo and UBMD Internal Medicine, Buffalo, NY
[h]Baylor College of Medicine, Houston, TX
[i]Medical College of Wisconsin, Milwaukee, WI
[j]Department of Medicine and the Gregory Flemming James Cystic Fibrosis Research Center, University of Alabama at Birmingham, Birmingham, AL

What was your research question?

In this study, we examined whether the lumacaftor/ivacaftor combination therapy would improve insulin secretion and glucose tolerance in people with CF who have two copies of the F508del CFTR (cystic fibrosis transmembrane conductance regulator) mutation.

Why is this important?

Glucose tolerance abnormalities including cystic fibrosis related diabetes (CFRD) are a well-known complication of CF. Currently, CFRD occurs in 15-20% of adolescents with CF and more than half of adults with CF. It has been suggested that the CFTR defect may play a direct or indirect role in insulin secretion. Lumacaftor/ivacaftor (brand name Orkambi) is a

combination drug that was approved to treat people with CF who have two copies of the F508del mutation by partially correcting the function of CFTR. Therefore, this trial was developed to examine whether treatment with lumacaftor/ivacaftor combination would improve insulin secretion and glucose tolerance.

What did you do?

Subjects who had CF and had been prescribed lumacaftor/ivacaftor by their CF care team at a CF Foundation's Therapeutic Development Network Center were recruited to the study. Participants included those with and without diagnosis of CFRD. The study participants underwent an oral glucose tolerance test (OGTT) prior to the first dose of lumacaftor/ivacaftor and this was their baseline measurement. The OGTT was repeated at 3, 6 and 12 months later whilst they were on lumacaftor/ivacaftor therapy. Samples for glucose and insulin levels were collected during OGTT and compared across the 4 time periods, to examine the impact of lumacaftor/ivacaftor therapy on glucose tolerance.

What did you find?

We had hypothesized that treatment with lumacaftor/ivacaftor would improve glucose tolerance parameters in this population. However, our hypothesis proved to be incorrect. Even after 12 months, overall the lumacaftor/invacaftor therapy did not improve insulin secretion or glucose tolerance in people with CF with two copies of the F508del mutation.

What does this mean and reasons for caution?

The likely explanation for the lack of observed benefit of lumacaftor/ivacaftor on glucose levels is that there is not enough improvement in CFTR activity with this particular drug to improve the function of insulin producing cells. In contrast, small studies in people with the CF G551D mutation, which is much easier to restore CFTR, have found that treatment does improve insulin secretion. It is still possible that lumacaftor/ivacaftor may have some modest beneficial effects in people with early stages of glucose intolerance that might be seen if a larger number of subjects was studied.

What's next?

Since the completion of this study, a new triple modulator therapy has been approved which is able to better correct CFTR function than lumacaftor/ivacaftor and other drugs are also under development. Future research with these new modulator therapies that result in greater CFTR recovery would provide more insights into the role of CFTR in development of glucose intolerance and CFRD.

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