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Cystic Fibrosis Research News

Title:

Effect of lumacaftor-ivacaftor on mucociliary clearance and clinical outcomes in cystic fibrosis: Results from the PROSPECT MCC sub-study

Lay title:
The effect of lumacaftor-ivacaftor on mucus clearance

Authors:

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What was your research question?

The approved CFTR modulator, lumacaftor-ivacaftor, is estimated to restore about 15% of normal CFTR function. We sought to determine whether this effect was enough to improve mucociliary clearance (MCC), and whether this would correlate with other improvements in lung health.

Why is this important?

Understanding the relationship between CFTR activity, MCC measurements, and clinical endpoints is critically important to our understanding of how much CFTR function is needed to improve clinical outcomes.

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What did you do?

We performed a prospective, longitudinal study of lumacaftor-ivacaftor in CF patients with two copies of the F508del CFTR mutation who were beginning treatment with this medication. Treatment effects over 1 month were assessed. We measured MCC using inhaled radioactive particles. Sweat chloride, lung function (spirometry), symptom scores, exhaled nitric oxide (NO), and lung clearance index (a marker of ventilation abnormality) were also measured. 25 subjects were enrolled.

What did you find?

Despite observing a small but significant improvement and sweat chloride, no improvement in MCC, spirometry, or any other endpoint was observed.

What does this mean and reasons for caution?

This study suggests that the modest increase in CFTR function that comes from treatment with lumacaftor ivacaftor was insufficient to cause improvements in multiple assessments of lung function (MCC, spirometry, lung clearance index) in this relatively small study. Although a larger studies have been able to show improvements in spirometry, lung clearance index, and exacerbation frequency, these data suggest that very small improvements in MCC, or an unrelated lung defense mechanism, is adequate to provide the protection against pulmonary exacerbations that was observed in earlier studies.

What's next?

The MCC assay will continue to be a valuable tool for the study of new CFTR-directed therapies, but only when the expected effect on CFTR is greater than that achieved by lumacaftor-ivacaftor. Additional research is needed to understand how restoring CFTR function protects against pulmonary exacerbations.

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