Cystic Fibrosis Research News

Title:

Lumacaftor/ivacaftor reduces exacerbations in adults homozygous for Phe508del mutation with severe lung disease

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What was your research question?

We performed a study to determine whether lumacaftor/ivacaftor would work as well in people with an FEV1 less than 40% predicted (ppFEV$_1$ < 40). We wanted to see if it would reduce the rate of acute worsening of lung infections (pulmonary exacerbations), improve lung function and see how well it was tolerated.

Why is this important?

Lumacaftor/Ivacaftor, is able to improve the functioning of the protein that is faulty in cystic fibrosis, in people with the most common genetic mutation known as delta F508 (Phe508del). In people with two copies of this gene, lumacaftor/ivacaftor results in a small but sustained improvement in lung function as measured by lung function testing (spirometry), fewer pulmonary exacerbations or chest infections, improved ability to gain and maintain weight. The effectiveness of lumacaftor/ivacaftor was only established in selected people. An important exclusion criterion was those with more severe lung disease, or an FEV1 of less than 40% predicted. Despite being excluded this is an important group of people who suffer

more severe symptoms and more frequent exacerbations. Recently concerns were raised that people with more severe disease were unable to tolerate lumacaftor/ivacaftor as well as those who were in the trials.

What did you do?

We performed a study to determine whether lumacaftor/ivacaftor would work as well in people with an FEV1 less than 40% predicted (ppFEV$_1$ < 40). We wanted to see if it would reduce the rate of pulmonary exacerbations, improve lung function and see how well it was tolerated. To understand this, we wanted to compare this effect to people with CF but who did not receive treatment with lumacaftor/ivacaftor. As we did not want to stop people with more severe lung disease from receiving lumacaftor/ivacaftor, we chose to compare the results of people who we started on lumacaftor/ivacaftor to people with CF, but who had another genetic mutation that meant lumacaftor/ivacaftor would not work. This is called a case control study.

What did you find?

We recruited 106 people with CF recruited from 7 Australian CF centres; 72 received lumacaftor/ivacaftor and 34 controls, were followed for 12 months. Treatment resulted in substantial reduction in the frequency of their pulmonary exacerbations over 12 months, that is a reduction of 55% compared to the controls as well as a longer time to first exacerbation requiring IV antibiotics. There was a small improvement in lung function seen in those who took the treatment, while the controls demonstrated a small decline over the 12 months of the study. The change in lung function though was too small and variable to clearly see a benefit.

Treatment however was poorly tolerated. The most common and serious complaint was symptoms of breathlessness or chest tightness. This was experienced by over half (55%) of all the people treated. This was so severe that 32% had to cease treatment altogether. Not surprisingly the benefits seen with treatment were not experienced in those who ceased it. The only risk factor that could be seen for this was lung function. Those with a lower FEV1 at the start were more likely to be unable to tolerate lumacaftor/ivacaftor.

What does this mean and reasons for caution?

Treatment with lumacaftor/ivacaftor despite its small effect on lung function was clearly very beneficial for those with severe lung disease, substantially reducing exacerbations. However, the side effects are unacceptably high. The more severe the impairment in lung function the less likely they were able to tolerate treatment.

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In contrast treatment with tezacaftor/ivacaftor has not been associated with these side effects, though it appears just as efficacious as lumacaftor/ivacaftor. Therefore, we recommend that tezacaftor/ivacaftor should be considered in preference to lumacaftor/ivacaftor in people with CF and FEV1 of less than 40%.

What's next?

Future trials of CFTR modulators should consider the effects of treatment in people with severe lung disease from cystic fibrosis. While changes in lung function in these people with CF are less likely other important benefits or unforeseen side effects may occur.

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