

Cystic Fibrosis Research News

Title:

Real-life initiation of lumacaftor/ivacaftor combination in adults with cystic fibrosis homozygous for the Phe508del *CFTR* mutation and severe lung disease

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What was your research question?

What is the short-term effectiveness of treatment with lumacaftor/ivacaftor combination in adults with cystic fibrosis (CF) and severe lung disease in a real-life setting? Are adverse events (mainly respiratory adverse events) and treatment discontinuation more frequent than in clinical trials in which patients had better lung function?

Why is this important?

Large placebo-controlled clinical trials have demonstrated that lumacaftor/ivacaftor combination treatment improved lung function and nutritional status, and decreased pulmonary exacerbations in people aged 12 years and older with CF homozygous for the

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Phe508del *CFTR* mutation. Nevertheless, those screened for recruitment in clinical trials were required to be in stable condition and no individual with severe lung function could be recruited. Because there is only limited experience with lumacaftor/ivacaftor outside of clinical trials and even less data on its safety and effectiveness in people with severe lung disease, we sought to obtain data on real-life initiation of lumacaftor/ivacaftor in such individuals.

What did you do?

Individuals with CF from 11 large French adult CF centres, who were homozygous for the Phe508del *CFTR* mutation, with a severe lung disease (e.g. forced expiratory volume in one second (FEV_1) $\leq 40\%$), and who initiated lumacaftor/ivacaftor treatment between January 2016 and June 2016, were included in a multicentre observational study. Adverse events (with a special attention to respiratory adverse events), treatment discontinuation, respiratory function and body mass index were investigated one month and three months after lumacaftor/ivacaftor initiation.

What did you find?

Among 53 individuals who started lumacaftor/ivacaftor, 16 participants (30%) discontinued treatment within three months, mainly due to respiratory adverse events (mainly chest tightness and breathlessness) ($n=13$). Adverse events were reported by 34 participants (64%), including respiratory symptoms in 27 participants (51%) (mainly chest tightness and breathlessness), gastrointestinal symptoms (abdominal pain, diarrhoea, nausea, and/or vomiting) in 9 participants (18%), fatigue, skin rash, and breast tension. Nineteen of these 34 participants (56%) remained on treatment. We found a gain in respiratory function after one end three months of treatment. After three months of treatment, the increase in FEV_1 was +3.19 % and 30% of participants had an increase of 5% or more. Nutritional status was unchanged.

What does this mean and reasons for caution?

Patients with CF and severe lung disease are more likely to experience respiratory symptoms (such as chest tightness and breathlessness) after initiation of treatment with lumacaftor/ivacaftor than those with better lung function who were included in the clinical trials. They are also more likely to discontinue lumacaftor/ivacaftor treatment in the first three months. Nevertheless, the individuals who continued treatment, including those with the most severe lung disease, had an increase in lung function comparable to what was



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observed in clinical trials. This justifies proposing the treatment to all eligible individuals, at the same time as bronchodilators in order to prevent respiratory symptoms.

What's next?

There is a need for better strategies to prevent respiratory adverse events associated with lumacaftor/ivacaftor and for the development of newer drugs with better safety profiles. Longer real-life evaluation of lumacaftor/ivacaftor is warranted to examine its safety profile and its effectiveness in preventing lung function decline and pulmonary exacerbations.

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