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Cystic Fibrosis Research News

Title:

Clinical response to lumacaftor-ivacaftor in patients with cystic fibrosis according to baseline lung function.

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What was your research question?

Our aim was to evaluate safety of effectiveness of lumacaftor-ivacaftor according to baseline lung function.

Why is this important?

Lumacaftor-ivacaftor (LUMA-IVA), a combination of CFTR modulators, is now licensed in many countries for people homozygous for the Phe508del *CFTR* mutation, who represent 40-50% of people with CF worldwide. Initial phase 3 clinical trials were undertaken in people with CF aged 12 years and older with a percent predicted forced expiratory volume in one second ($ppFEV_1$) between 40 and 90. Nonetheless, LUMA-IVA was approved for Phe508del homozygous individuals at all levels of $ppFEV_1$ by regulatory agencies in the US and in Europe. Few data exist on 1-year safety and effectiveness in people with $ppFEV_1<40$ or ≥ 90.

What did you do?

The present study used data collected in a large cohort of people aged 12 years and older who started LUMA-IVA in 2016 in France, in order to examine its safety and effectiveness at different levels of baseline $ppFEV_1$ over the first year of treatment. Among the 845 individuals who initiated LUMA-IVA in 2016, one third of those had a $ppFEV_1$ at baseline that would have been considered either too low ($ppFEV_1<40$) or too high ($ppFEV_1\geq 90$) to meet eligibility criteria for phase 3 clinical trials, which included only people with $ppFEV_1$ [40-90[.

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What did you find?

A $ppFEV_1$ increase ≥5% was found in 40% of people with baseline $ppFEV_1$ [40-90[, a proportion that was 1.5 to 2-fold higher than in those with baseline $ppFEV_1$ <40 or $ppFEV_1$≥90. Improvement in body mass index (BMI) was found in all individuals, and the magnitude of improvement was comparable across all subgroups. The number of intravenous (IV) antibiotic days per year was also reduced in all subgroups, but the effects of LUMA-IVA on exacerbation rates appeared less robust in people with severe respiratory damage. As expected, respiratory adverse events occurred more often in those with more severe respiratory disease.

What does this mean and reasons for caution?

The present analysis indicates that adolescents and adults with CF may benefit from LUMA-IVA at all levels of baseline lung function. Findings that the subgroup of people with $ppFEV_1$<40 were at higher risk of adverse effects, and that both subgroups of patients with $ppFEV_1$<40 or with $ppFEV_1$≥90 showed less consistent improvement in lung function concur with the choice of limiting recruitment in phase 3 clinical trials to people with $ppFEV_1$ [40-90[. Importantly, at the individual level, those with $ppFEV_1$<40 or $ppFEV_1$≥90 could show a significant improvement in $ppFEV_1$ after initiation of CFTR modulator therapy.

What's next?

These findings reinforce the decision from regulatory agencies to grant treatment indication to all people with eligible *CFTR* genotypes, regardless of baseline lung function.

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