Journal of Cystic Fibrosis
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CYSTIC FIBROSIS FOUNDATION
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Citation:

Konstan MW, McKone EF, Moss RB, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. Lancet Respir Med. 2017 Feb;5(2):107-118.

What was your research question?

What is the long-term safety profile and treatment effectiveness of lumacaftor/ivacaftor (Orkambi) therapy in cystic fibrosis patients homozygous for the F508del CFTR mutation?

Why is this important?

Combination lumacaftor/ivacaftor is the first therapy that directly targets the underlying cause of cystic fibrosis in patients homozygous for the F508del-CFTR mutation. Long-term efficacy and safety have not yet been assessed. The rate of lung function decline is a useful measure of disease trajectory in patients with cystic fibrosis, so determining the impact of lumacaftor/ivacaftor on lung function decline will show whether treatment has a long-term disease-modifying effect.

What did you do?

Patients in one of two previous clinical trials of lumacaftor/ivacaftor (TRAFFIC and TRANSPORT) were invited to enroll in PROGRESS, a 96-week extension study. All PROGRESS patients received 1 of 2 dosing regimens of lumacaftor/ivacaftor. Patients who received lumacaftor/ivacaftor in a previous trial received the same dose as during those trials. Patients who previously received placebos were randomly assigned to one of two dosage regimens in PROGRESS. We mainly studied lumacaftor/ivacaftor safety and took several

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measurements to determine lumacaftor/ivacaftor effectiveness: lung function, body mass index (BMI), patient surveys on how they were feeling, and number of pulmonary exacerbations during the trial.

What did you find?

Results from this trial were similar to previous trials of lumacaftor/ivacaftor. Most adverse events were mild or moderate. Chest tightness and difficulty breathing were more common in patients initiating lumacaftor/ivacaftor than in those continuing it. Most adverse respiratory events reported by those transitioning from placebo resolved within two weeks of starting treatment. A small increase in blood pressure was noted. Improvements were seen in BMI and patient-reported respiratory symptoms. Lung function stayed similar to baseline. Rate of pulmonary exacerbations decreased and rate of lung function decline slowed compared to similar patients from the Patient Registry who did not take lumacaftor/ivacaftor.

What does this mean and reasons for caution?

These data indicate that extended treatment with lumacaftor/ivacaftor is generally safe and well tolerated. Improved rates of change in lung function, pulmonary exacerbations, and nutritional status suggest that lumacaftor/ivacaftor may have a longer-term disease-modifying effect. PROGRESS was not a placebo-controlled study and so those patients on the study drug were not compared to a separate group enrolled in the study who were not taking the medication. As the combined study duration (TRAFFIC/TRANSPORT plus PROGRESS) was only 120 weeks, risks and benefits over the longer term have not yet been established.

What's next?

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As lumacaftor/ivacaftor is now commercially available, real-world studies are ongoing to monitor the long-term safety and efficacy of lumacaftor/ivacaftor treatment. Relationships between the short-term benefits and long-term disease-modifying effects of lumacaftor/ivacaftor and the long-term predictability of disease modification based on short-term benefits are also being investigated.