primary studies - published RCT

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.

Code: PM28011037 **Year:** 2016 **Date:** 2016 **Author:** Konstan MW

Study design (if review, criteria of inclusion for studies)

Phase 3, parallel-group, multicentre, 96-week study

Participants

Patients who completed TRAFFIC or TRANSPORT in 191 sites in 15 countries. Patients were eligible if they were at least 12 years old with cystic fibrosis and homozygous for the F508del-CFTR mutation. Exclusion criteria included any comorbidity or laboratory abnormality that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering the study drug to the participant, history of drug intolerance, and history of poor compliance with the study drug.

Interventions

Patients who previously received active treatment in TRANSPORT or TRAFFIC remained on the same dose in PROGRESS. Patients who had received placebo in TRANSPORT or TRAFFIC were randomly assigned (1:1) to receive lumacaftor (400 mg every 12 h)/ivacaftor (250 mg every 12 h) or lumacaftor (600 mg once daily)/ivacaftor (250 mg every 12 h).

Outcome measures

The primary outcome was to assess the long-term safety of combined therapy. The estimated annual rate of decline in percent predicted FEV1 (ppFEV1) in treated patients was compared with that of a matched registry cohort. Efficacy analyses were based on modified intention-to-treat, such that data were included for all patients who were randomly assigned and received at least one dose of study drug.

Main results

Between Oct 24, 2013, and April 7, 2016, 1030 patients from the TRANSPORT and TRAFFIC studies enrolled in PROGRESS, and 1029 received at least one dose of study drug. 340 patients continued treatment with lumacaftor 400 mg every 12 h/ivacaftor 250 mg every 12 h; 176 patients who had received placebo in the TRANSPORT or TRAFFIC studies initiated treatment with lumacaftor 400 mg every 12 h/ivacaftor 250 mg every 12 h, the commercially available dose, for which data are presented. The most common adverse events were infective pulmonary exacerbations, cough, increased sputum, and haemoptysis. Modest blood pressure increases seen in TRAFFIC and TRANSPORT were also observed in PROGRESS. For patients continuing treatment, the mean change from baseline in ppFEV1 was 0.5 (95% CI -0.4 to 1.5) at extension week 72 and 0.5 (-0.7 to 1.6) at extension week 96; change in BMI was 0.69 (0.56 to 0.81) at extension week 72 and 0.96 (0.81 to 1.11) at extension week 96. The annualised pulmonary exacerbation rate in patients continuing treatment through extension week 96 (0.65, 0.56 to 0.75) remained lower than the placebo rate in TRAFFIC and TRANSPORT. The annualised rate of ppFEV1 decline was reduced in lumacaftor/ivacaftor-treated patients compared with matched controls (-1.33, -1.80 to -0.85 vs -2.29, -2.56 to -2.03). The efficacy and safety profile of the lumacaftor 600 mg once daily/ivacaftor 250 mg every 12 h groups was generally similar to that of the lumacaftor 400 mg every 12 h/ivacaftor 250 mg every 12 h groups.

Authors' conclusions

The long-term safety profile of lumacaftor/ivacaftor combination therapy was consistent with previous RCTs. Benefits continued to be observed with longer-term treatment, and lumacaftor/ivacaftor was associated with a 42% slower rate of ppFEV1 decline than in matched registry controls.

http://dx.doi.org/10.1016/S2213-2600(16)30427-1

See also

Lancet Respir Med. 2016 Dec 20. pii: S2213-2600(16)30427-1. doi: 10.1016/S2213-2600(16)30427-1.

Keywords

Adult; Aged; CFTR Modulators; Genetic Predisposition to Disease; pharmacological_intervention; placebo; VX-770; VX-809; lumacaftor; Aminophenols; Orkambi; ivacaftor;