

ONLINE SUPPLEMENTARY MATERIAL

Inclusion and exclusion criteria

This study included 10 patients with CF and a class III *CFTR* gating mutation (p.G551D, p.G178R) on at least one allele. This represents approximately 20% of patients 6 years of age and older with a class III *CFTR* gating mutation in Toronto. Individuals with acute respiratory symptoms, acute respiratory infection, or a chronic lung disease not related to CF were excluded, as were individuals requiring supplemental oxygen. All patients received 150 mg ivacaftor tablets twice daily. Adherence was not measured.

MBW_{N2} and spirometry

MBW_{N2} was performed in triplicate using an open circuit, bias flow system (Exhalyzer D®, EcoMedics AG, Duernten, Switzerland) and associated software (Spiroware® 3.1 EcoMedics AG). MBW_{N2} trials were performed and over-read for quality control according to guidelines proposed in the ERS/ATS consensus statement.[1] Spirometry was performed according to American Thoracic Society (ATS) standards using the Vmax system (VIASYS CareFusion, San Diego, California, USA).[2,3] FEV₁ was converted to percent predicted using the Global Lung Function Initiative reference equations.[4]

Additional outcomes

Secondary MBW_{N2} outcomes included moment ratios and LCI calculated at 5% of the normalized starting end-tidal concentration of nitrogen (LCI₅). Moment ratios (M_1/M_0 and M_2/M_0) were calculated for both the end of the washout (2.5% of the normalized starting end-tidal concentration of nitrogen) and for 6 turnovers (6 TO), representing an earlier time point of the washout.[5-7] All six MBW outcomes showed significant improvement over time, even after adjustment for baseline values (Table S1). While earlier cut-offs have the advantage of shorter washout time, there is a trade-off with sensitivity of treatment efficacy.[5] In the case of ivacaftor, significant improvements in all outcomes were observed within the first month, suggesting that earlier cut-offs may be appropriate for experimental compounds with large treatment effects. Further investigation into the potential advantages of using an earlier cut-off for MBW_{N2} has been discussed in recent publications and is ongoing.[5, 8-10]

Additional results

Table S1. Summary of paired t-test results and GEE results where the outcome was estimated as a function of time (i.e. time⁻² for MBW measurements and time² for FEV₁ % predicted). Results were similar when a mixed-effects model was used.

Outcome	Mean difference from baseline at 1 month		Unadjusted GEE model		GEE model adjusted for baseline	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value	Estimate (95% CI)	P value
LCI _{2.5}	-2.15 (-3.05 to -1.26)	<0.001	2.76(2.23 to 3.29)	<0.001	2.32(1.74 to 2.89)	<0.001
LCI ₅	-0.87 (-1.46 to -0.29)	0.008	1.16(0.71 to 1.61)	<0.001	1.04(0.66 to 1.43)	<0.001
M ₁ /M ₀	-0.42 (-0.61 to -0.22)	0.001	0.564(0.427 to 0.700)	<0.001	0.504(0.380 to 0.627)	<0.001
M ₂ /M ₀	-5.17 (-7.59 to -2.74)	0.001	7.01(5.36 to 8.66)	<0.001	6.67(4.54 to 8.80)	<0.001
M ₁ /M ₀ at 6 TO	-0.06 (-0.11 to -0.01)	0.02	0.084(0.043 to 0.124)	<0.001	0.068(0.038 to 0.098)	<0.001
M ₂ /M ₀ at 6 TO	-0.33 (-0.59 to -0.07)	0.02	0.456(0.249 to 0.664)	<0.001	0.386(0.232 to 0.541)	<0.001
FEV ₁ % predicted	11 (2 to 20)	0.02	0.143(0.058 to 0.228)	<0.001	0.205(0.127 to 0.283)	<0.001

References

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