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Ivacaftor in severe cystic fibrosis lung disease and a G551D mutation

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Abstract

Ivacaftor is gene-specific oral therapy for patients with cystic fibrosis who have a cystic fibrosis transmembrane conductance regulator mutation, G551D. To date, limited information is available about the benefit in patients with severe CF related lung disease, as such patients were excluded from the phase III trials. We report the early results on clinical outcomes, sweat electrolytes and C-reactive protein in three adults with a G551D mutation and advanced lung disease. A mean increase of 6% in FEV_1 was observed at 2 weeks and a mean reduction in sweat chloride of −48.9 mmol/L. While improvements in spirometry, weight gain and reduction in sweat electrolytes are similar with those reported in the phase III trials, a formal comparison was not performed.

Introduction

The G551D mutation affects 4% of the cystic fibrosis (CF) population internationally and is the second most common mutation affecting 8% of patients in Australia [1]. Ivacaftor (Kalydeco™, Vertex Pharmaceuticals, Cambridge, MA, USA) is a gene-specific oral, cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, which augments chloride transport activity of G551D-*CFTR* protein function in vitro. In two recent multicenter trials in patients with at least one G551D mutation, Ivacaftor was associated with improvements in lung function, reduced pulmonary exacerbations, improvement in patient-reported respiratory symptoms, increased weight and a reduction in sweat chloride over 48 weeks [2, 3]. Both trial excluded patients with severe airflow obstruction (FEV_1 < 40% predicted). Inclusion criteria included upper limit of FEV_1 of 90% predicted in the adult/adolescent study (≥12 years of age) and 105% predicted in the study of children (≥6 and <12 years of age) [2, 3].

In 2012, Ivacaftor was made available in Australia on compassionate grounds. In this case series of three adults with a G551D-*CFTR* mutation, we report the use of Ivacaftor in CF patients with severe lung disease.

Case Report

Three patients with F508del/G551D mutations (two female) with mean age 29.0 (4.5) years were commenced on Ivacaftor. The mean (standard deviation [SD]) baseline FEV_1 (% predicted) was 37 (14). Two patients were being assessed for lung transplant due to high treatment burden (intravenous [IV] antibiotic dependence). Clinical and laboratory assessments were performed at baseline, 2 weeks, monthly (1–4 months) then at 6 months and included: spirometry, weight, sweat electrolytes, 6-min walk test, Cystic Fibrosis Questionnaire-Revised (CFQ-R). Blood was collected for C-reactive protein (CRP), chemistry and full blood count. Hospital days and IV antibiotic days were

recorded for 6 months prior and following commencement of Ivacaftor.

Patient 1 was unable to complete all study procedures from week 8 because of injuries sustained in a motor vehicle accident (Day 54), and due to Ivacaftor interruption (adverse event).

A mean increase of 6% in FEV_1 was observed at 2 weeks (Fig. 1a), accompanied by a mean improvement in 6-min walk distance of 29 m. Weight gain was seen and the patients that completed 6-month visits had 3.7 kg and 5.4 kg increases (Fig. 1b). The mean (SD) sweat chloride value at baseline was 102 mmol/L (8.5). At 2 weeks, there was a mean reduction in sweat chloride of −48.9 mmol/L. The reduction in sweat chloride was sustained (Fig. 1c).

All patients reported improvements in respiratory symptoms. There was a minimum clinically important difference of four units change in the respiratory domain of the CFQ-R in all patients at 8 weeks. In two patients with high treatment burden and associated high inflammatory levels prior to Ivacaftor, median CRP was reduced and in parallel, a reduction in hospital and IV antibiotic requirements (Table 1). As a consequence, transplant listing has been deferred in both cases.

An adverse event of rash (day 2) was observed in Patient 2 and also elevated liver enzymes (day 160) in Patient 1, which necessitated temporary drug withdrawal. Ivacaftor was subsequently re-introduced without recurrence and was considered to relate to either beta-lactam antibiotics (meropenem) and/or an intercurrent viral infection. In both cases, the events were considered unlikely related to Ivacaftor.

Discussion

We provide a description of patients with advanced lung disease commenced on Ivacaftor. Despite the severity of lung disease in this group of patients, improvements in clinical and biochemical outcomes were similar to those described in the earlier phase III clinical trials. Ivacaftor is the first CFTR mutation-specific therapy to demonstrate improvements in clinical outcomes for patients with CF. Entry into each randomized control trial required mild to moderate lung

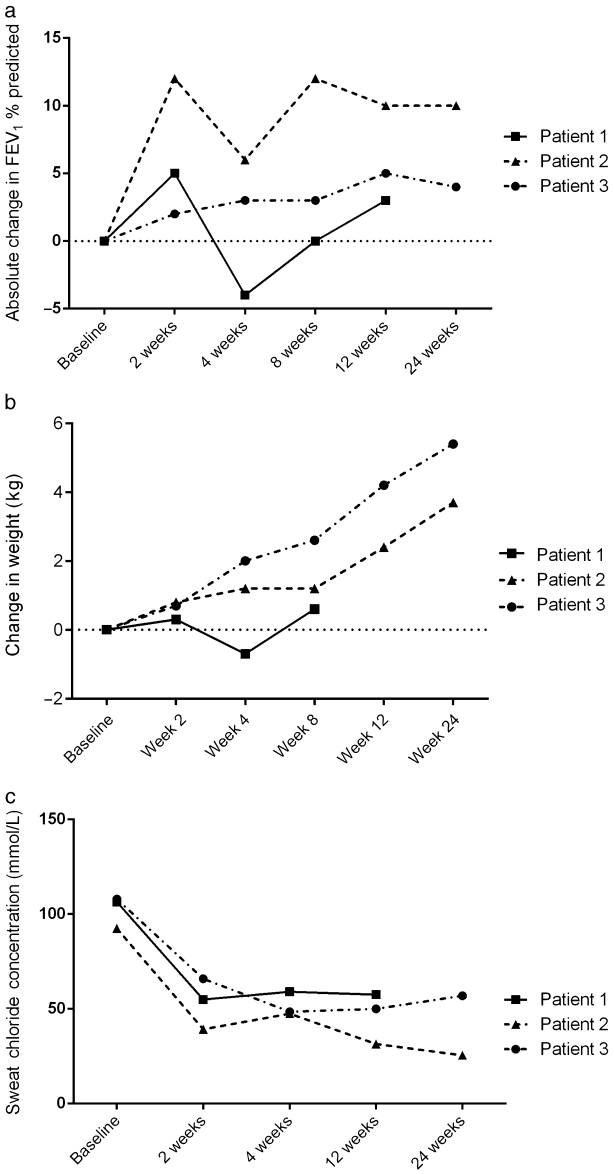

Figure 1. Change from baseline in, (a) FEV_1 percentage predicted, (b) Weight and (c) Sweat chloride concentration.

Table 1. C-reactive protein (CRP) and intravenous (IV) antibiotic days.

	6 months prior to ivacaftor				6 months after ivacaftor			
	# tests	Median CRP	CRP range	IV antibiotic days	# tests	Median CRP	CRP range	IV antibiotic days
Patient 1	18	37.7	13–154	105	16	29.9	6–113	59
Patient 2	9	63.8	13–122	56	8	47.7	19–72	15
Patient 3	4	17.8	2.2–28	11	5	14.9	11–22	0

disease (e.g., FEV_1 above 40% predicted and also a period of clinical stability prior to recruitment) [2, 3].

The Special Access Program (called Named Patient Program) supported by Vertex Pharmaceuticals commenced in July 2011 allowing compassionate access to Ivacaftor for patients with severe lung disease. Approval was sought from Vertex, the Hospital Administration and the Human Research Ethics Committee at The Prince Charles Hospital, Brisbane to access Ivacaftor for use in three patients with severe lung disease. Treatment has resulted in significant improvements in clinical outcomes, in particular in weight gain, reduction in hospitalization episodes and total time on IV antibiotics. In parallel, there was a decrease in sweat chloride concentrations similar to the extent reported in the earlier clinical trials in patients with milder lung disease. Improvements in patient reported respiratory outcomes and an increase in the 6-min walk distance were observed.

In the only published case series to date of the use of Ivacaftor in a patient with severe lung disease, improvement in FEV_1 mirrored those experienced in our patient group and no severe adverse events were noted [4]. Our series adds to this experience by demonstrating reduction in sweat electrolytes, improved exercise tolerance and patient reported respiratory symptoms were demonstrated, suggesting lung function may not be the best outcome measure in patients with severe disease.

These cases demonstrate that Ivacaftor is generally well tolerated in patients with severe lung disease and results in improvements in clinical and patient reported outcomes. It remains unclear as to whether for this group of patients Ivacaftor should be used as a bridge to transplantation or as a way of delaying transplantation.

Disclosure Statements

A conflict of interest was declared as follows: Scott Bell (Chief Investigator) and Michelle Wood (Clinical Trial Coordinator) have participated in clinical trials sponsored by Vertex Pharmaceuticals and have received travel support to attend investigator meetings. Scott Bell is a Member of the Writing group for Vertex for a Clinical Trial Program.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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