Journal of Cystic Fibrosis 16 (2017) 41 – 44

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Short Communication

Correlation of sweat chloride and percent predicted FEV_1 in cystic fibrosis patients treated with ivacaftor☆

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Received 2 August 2016; revised 30 September 2016; accepted 1 October 2016
Available online 20 October 2016

Abstract

Ivacaftor, a CFTR potentiator that enhances chloride transport by acting directly on CFTR to increase its channel gating activity, has been evaluated in patients with different CFTR mutations. Several previous analyses have reported no statistical correlation between change from baseline in $ppFEV_1$ and reduction in sweat chloride levels for individuals treated with ivacaftor. The objective of the post hoc analysis described here was to expand upon previous analyses and evaluate the correlation between sweat chloride levels and absolute $ppFEV_1$ changes across multiple cohorts of patients with different CF-causing mutations who were treated with ivacaftor. The goal of the analysis was to help define the potential value of sweat chloride as a pharmacodynamic biomarker for use in CFTR modulator trials. For any given study, reductions in sweat chloride levels and improvements in absolute $ppFEV_1$ were not correlated for individual patients. However, when the data from all studies were combined, a statistically significant correlation between sweat chloride levels and $ppFEV_1$ changes was observed ($p < 0.0001$). Thus, sweat chloride level changes in response to potentiation of the CFTR protein by ivacaftor appear to be a predictive pharmacodynamic biomarker of lung function changes on a population basis but are unsuitable for the prediction of treatment benefits for individuals.

Keywords: Cystic fibrosis; Ivacaftor; Sweat chloride; FEV_1

Cystic fibrosis (CF) is an autosomal recessive hereditary multi-organ disease caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene [1,2]. CFTR regulates ion flux at the surface of certain epithelial cells, and the decreased CFTR-mediated ion transport in CF results in a wide range of symptoms, including abnormal electrolyte concentrations in the sweat of patients with CF [3].

Ivacaftor, a CFTR potentiator that enhances chloride transport by acting directly on CFTR to increase its channel gating activity, has been evaluated in patients with different *CFTR* mutations [4–8]. In a Phase 2 study of patients carrying the *G551D* mutation on at least one allele, administration of ivacaftor resulted in an early and substantial mean decrease in sweat chloride levels, as well as early improvements in lung function as measured by percent predicted forced expiratory volume in 1 s ($ppFEV_1$) [9,10]. A dose-dependent effect was seen on sweat chloride levels with ivacaftor treatment (25 mg to 250 mg) in this trial [10], suggesting that sweat chloride may also correlate with $ppFEV_1$. Seliger et al. conducted a post hoc analysis of two double-blind, multicenter studies to investigate the value of sweat

Abbreviations: CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator; CI, confidence interval; $ppFEV_1$, percent predicted forced expiratory volume in 1 s; q12h, every 12 h.

☆ **Previous Presentations**: A portion of the data in this manuscript was presented previously at the 2015 NACFC annual meeting and is cited as: Fidler M, Beusmans J, Panorchan P, Van Goor F. Correlation of sweat chloride and percent predicted FEV_1 in cystic fibrosis patients treated with ivacaftor. Pediatr Pulmonol 2015:50, S41, S193–S453.

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http://dx.doi.org/10.1016/j.jcf.2016.10.002

chloride level changes in predicting improvements in pulmonary function in individuals with CF carrying at least one copy of the *G551D–CFTR* mutation treated with ivacaftor [4,5,11]. The analysis showed no statistical correlation between change from baseline in $ppFEV_1$ and reduction in sweat chloride levels for individuals [11], thus confirming data previously published by Durmowitz et al. [12]. The efficacy of ivacaftor has also been evaluated in patients harboring numerous other mutations [7,8] who were predicted to respond to ivacaftor therapy based on in vitro data [13] and in patients homozygous for the *F508del* mutation [6] who were not expected to show a clinically meaningful response based on in vitro response data [13].

The objective of the post hoc analysis described here was to expand upon previous analyses and evaluate the correlation between sweat chloride levels and absolute $ppFEV_1$ changes across multiple cohorts of patients with different CF-causing mutations who were treated with ivacaftor. The goal of the analysis was to help define the potential value of sweat chloride as a pharmacodynamic biomarker for use in CFTR modulator trials. Eight Phase 2 and 3 clinical studies contributed data to this analysis of the relationship between sweat chloride levels and $ppFEV_1$ among patients with CF treated for at least 14 days with ivacaftor monotherapy. Trial information and treatment details for the eight studies are shown in Table 1.

For any given study, reductions in sweat chloride levels and improvements in absolute $ppFEV_1$ were not correlated for individual patients [6]. However, when the data from all studies were combined, a statistically significant correlation between sweat chloride levels and $ppFEV_1$ changes was observed ($p < 0.0001$). In Fig. 1, each data point corresponds to a particular study and dose and marks the mean absolute change from baseline (and 95% confidence interval [CI]). Only patients with complete data, i.e, who had baseline and end-of-treatment values for $ppFEV_1$ and sweat chloride were included in the analyses. For study 110 (*R117H*) [7] patients aged <18 years were excluded since baseline FEV_1 values were considered normal; the remaining patients were stratified according to their confirmed 5T/7T status and plotted separately in the graph. Patients in study 111 had a mixed group of non-*G551D* gating CFTR mutations [8]. Responses in patients with the *G970R* mutation, excluded from the analyses, were not consistent with those seen in the other gating mutations and research into this mutation type is ongoing.

Each data point corresponds to a particular study and shows the mean absolute change (and its 95% CI) from baseline in percentage points for FEV_1. In all studies, patients were treated with ivacaftor 150 mg q12h, except for study 101 in which patients were treated with one of four doses of ivacaftor (25, 75, 150, or 250 mg) q12h plotted individually. Relative sample size is indicated by symbol size in the figure. Solid line shows the fit of the weighted linear model (weighted by number of patients in each study); $r^2 = 0.889$, $p < 0.0001$, slope = −0.168 [95% CI: −0.21, −0.13], intercept = 0.95 [95% CI: −0.56, 2.51]. Dashed lines show the 95% CI of the fit.

CF, cystic fibrosis; CI, confidence interval; $ppFEV_1$, percent predicted forced expiratory volume in 1 s; q12h, every 12 h.

Fig. 2 depicts the absolute changes from baseline in $ppFEV_1$ and sweat chloride levels for each individual patient enrolled in the eight clinical trials analyzed. The statistically significant correlation between sweat chloride levels and $ppFEV_1$ changes observed for mean values across the full dataset of studies was also observed for individual changes ($p < 0.0001$, for both).

Each data point corresponds to an individual study participant and shows the absolute change from baseline in percentage points for FEV_1 plotted against absolute change in sweat chloride. Straight lines show fit obtained by linear regression. Contours correspond to levels of data density and show consistent correlation and reinforce the observed trend line. The red line represents the LOESS regression. In all studies, patients were treated with ivacaftor 150 mg q12h, except for study 101 in which patients were treated with four doses of ivacaftor (25, 75, 150, or 250 mg) q12h. Pearson correlation: −0.339 [95% CI: −0.429, −0.241]; linear fit: slope = −0.115, intercept = 2.48, $p < 0.0001$.

Table 1
Study-level features of the post hoc analysis describing the correlation between sweat chloride levels and absolute $ppFEV_1$ changes in patients with CF who received ivacaftor in clinical studies.

Trial identification number	Age (y)	N[a]	Mutation	Treatment regimen
VX770-101 [10]	≥18	42	*G551D*	Part A: ivacaftor 25, 50, 75, or 150 mg q12h for 14 d Part B: ivacaftor 150 or 250 mg q12h for 28 d
VX770-102 [4]	≥12	78	*G551D*	Ivacaftor 150 mg q12h for 48 wks
VX770-103 [5]	6–11	23	*G551D*	Ivacaftor 150 mg q12h for 48 wks
VX770-104 [6]	≥12	107	*F508del* homozygous	Ivacaftor 150 mg q12h for 16 wks[b]
VX770-106 [14]	≥6	17	*G551D*	Ivacaftor 150 mg q12h for 28 days
VX770-110 [7]	≥6 Patients aged <18 years were excluded from analysis[c]	18	*R117H*	Ivacaftor 150 mg q12h for 24 wks[b]
VX770-111 [8]	≥6	32	All non-*G551D* gating mutations except *G970R*	Ivacaftor 150 mg q12h for 8 wks[b]
VX770-113 [14]	≥12	21	Clinical evidence of CFTR residual function	Ivacaftor 150 mg q12h

CF, cystic fibrosis; $ppFEV_1$, percent predicted forced expiratory volume in 1 s; q12h, every 12 h.

[a] Of the 353 patients identified, 338 patients had baseline and end-of-treatment values for $ppFEV_1$ and sweat chloride and were included in the analyses. Four patients with *G970R* were excluded, as were patients with *R117H* who did not have confirmed 5T or 7T status.

[b] Eligible patients had the opportunity to participate in an open-label extension study.

[c] Remaining patients were stratified according to confirmed 5T/7T status. One outlying patient with an immediate and continuing decrease of >20% in $ppFEV_1$ who discontinued after week 8 was excluded.