Journal of Cystic Fibrosis 14 (2015) 727 – 732

www.elsevier.com/locate/jcf

Original Article

Effect of ivacaftor therapy on exhaled nitric oxide in patients with cystic fibrosis

Hartmut Grasemann [a,c,*], Tanja Gonska [b,c], Julie Avolio [b], Michelle Klingel [c], Elizabeth Tullis [d], Felix Ratjen [a,c]

[a] Division of Respiratory Medicine, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Canada
[b] Division of Gastroenterology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Canada
[c] Program in Physiology and Experimental Medicine, SickKids Research Institute, The Hospital for Sick Children, University of Toronto, Toronto, Canada
[d] Division of Respirology and Keenan Research Centre of Li Ka Shing Knowledge Institute, Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, Canada

Received 29 April 2015; revised 30 June 2015; accepted 1 July 2015
Available online 11 July 2015

Abstract

Airways of patients with cystic fibrosis are deficient for nitric oxide. Low nitric oxide in cystic fibrosis has been shown to be associated with poor pulmonary function and risk of infection with certain pathogens. Treatment of cystic fibrosis patients with the cystic fibrosis transmembrane conductance regulator (CFTR)-targeting drug ivacaftor results in improved pulmonary function. The effect of ivacaftor on airway nitric oxide has not been assessed.

Methods: In this observational trial, fractional exhaled nitric oxide (FE_{NO}) was measured before and 4 weeks after initiation of ivacaftor therapy, in patients with cystic fibrosis and a CFTR gating mutation. The effect of ivacaftor on FE_{NO} was compared to treatment with inhaled dornase alfa or hypertonic saline for 4 weeks, respectively.

Results: A total of 15 patients on ivacaftor therapy were studied. Pulmonary function improved significantly and mean (±SD) FE_{NO} increased from 8.5 ± 5.0 to 16.2 ± 15.5 ppb. The effect was more pronounced in pediatric compared to adult patients. There was no linear correlation between changes in FE_{NO}, pulmonary function or sweat chloride concentration. Neither treatment with inhaled dornase alfa (n = 15) or hypertonic saline (n = 16) resulted in a change in FE_{NO}.

Conclusion: Therapy with ivacaftor results in an increase in nitric oxide formation in cystic fibrosis airways, while dornase alfa or hypertonic saline has no effect on airway nitric oxide. Some beneficial effects of CFTR targeting therapy in CF may result from improved airway nitric oxide production.

© 2015 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.

Keywords: Cystic fibrosis; Ivacaftor; Pulmonary function; Nitric oxide

1. Introduction

Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, and del508F-CFTR is the most common CF causing mutation in Caucasians. CFTR dysfunction results in decreased transepithelial chloride secretion and an imbalance in the epithelial electrolyte and water homeostasis. In the CF airways this imbalance causes dehydration and retention of mucus which contributes to the vicious cycle of inflammation and infection, ultimately causing respiratory failure [1]. Patients with CF often have reduced airway nitric oxide (NO) levels, and low fractional exhaled NO (FE_{NO}) has been shown to be associated with poor pulmonary function and an increased risk for infections with certain CF pathogens, including

* Corresponding author at: The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.

http://dx.doi.org/10.1016/j.jcf.2015.07.001
1569-1993/© 2015 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.

Pseudomonas aeruginosa [2–4]. The reasons for the decrease in CF airway NO are not completely understood and may be related to the reduced expression of iNOS in airway epithelium [5–7], or abnormalities in the L-arginine and NO metabolism [8–10].

Endogenous NO production also plays a role in the downregulation of sodium absorption and can lead to an increase in CFTR independent and CFTR related transepithelial chloride secretion [11,12]. Treatment with the NO-donor S-nitrosoglutathione (GSNO) promotes maturation of delF508-CFTR and increases chloride efflux, both in CF cell lines and in primary nasal epithelial cells from delF508-CF patients [13]. Thus, improving CFTR function in patients with CF could lead to increased airway NO and improving NO deficiency could have beneficial effects on CF epithelial chloride secretion.

Recently, ivacaftor, has been approved as the first CFTR-targeting drug for treatment in people with CF and certain gating mutations, of which G551D is the most frequent [14,15]. Given the link between CFTR dysfunction and low airway NO, the aim of this study was therefore to assess whether ivacaftor therapy in patients with CF and a CFTR gating mutation will lead to an increase in FE_{NO}.

2. Methods

Patients were included in this observational trial if they had a confirmed diagnosis of CF and were eligible for treatment with ivacaftor. Patients were recruited from two study sites, the Hospital for Sick Children and St. Michael's Hospital, in Toronto, Ontario. The study was approved by both Institutional Research Ethic Boards (Hospital for Sick Children's REB #1000036224 and St. Michael's Hospital REB #13-089). Written informed consent was obtained by all participating patients or their legal guardian(s). Standard pulmonary function testing, sweat chloride testing and measurement of FE_{NO} were performed before and 4 weeks after initiation of ivacaftor therapy.

To compare the effects of ivacaftor on FE_{NO} and pulmonary function with other treatments we used FE_{NO} and spirometry data from two previously published clinical trials (Hospital for Sick Children's REB #1000024909 and REB #1000010903) [16,17]. These two studies were designed to determine if the lung clearance index (LCI) could detect a treatment response to either dornase alfa or hypertonic saline in pediatric CF patients with normal spirometry. FE_{NO} was measured during regular study visits but these measures were not included in previous analyses or publications. For both studies, eligible patients had to have a confirmed diagnosis of CF, be between 6 and 18 years of age, able to perform reproducible spirometry, have a baseline $FEV_1 \geq 80\%$ predicted at the screening visit and an oxyhemoglobin saturation of $\geq 90\%$ in room air. Both studies were designed as crossover placebo-controlled trials of four weeks of each intervention in a randomized sequence separated by a four week washout. Only the active treatment periods in patients having paired measurements of FE_{NO} before and after therapy were included in this analysis. The interventions consisted of either 2.5 ml of dornase alfa or 4 ml of 7% hypertonic saline (HS) twice daily for four weeks [16,17].

Participants performed spirometry according to the American Thoracic Society (ATS) guidelines [18] using a mass flow sensor (Vmax series, SensorMedics Corporation, Yorba Linda, California, USA). The fraction of exhaled NO (FE_{NO}) was measured using a chemiluminescence analyzer (Eco Physics CLD 88 sp® NO analyzer, Dürnten, Switzerland). Single breath on-line measurements were performed at a constant expiratory flow of 50 ml × min^{-1}, ($FE_{NO\ 50}$) in accordance with published European Respiratory Society (ERS)/ATS standards [19]. The mean of three measurements within 15% variation was used for analysis.

2.1. Statistical analyses

Results were expressed as means ± standard deviations (SD), unless stated otherwise. Comparisons were made with two-tailed student's t-tests for normally distributed data or Wilcoxon Rank Sum tests for non-parametric data, where appropriate. Paired t-tests were used to compare results before and after treatment; Wilcoxon Sign-Rank tests were used for non-parametric data. The Spearman correlation coefficient was used to assess correlations between continuous variables. p-Values < 0.05 were considered significant. All statistical analyses were conducted using GraphPad Prism 4.0c (GraphPad Software Inc., La Jolla, CA, USA).

3. Results

A total of 15 patients (8 adult and 7 children) treated with ivacaftor were included in this study. Baseline characteristics of the study population are shown in Table 1. Pulmonary function data before and four weeks after initiation of treatment are shown in Table 2. FVC ($p = 0.0003$), FEV_1 ($p = 0.0001$) and $FEF_{25–75}$ ($p = 0.004$) increased significantly in the ivacaftor treated patients, and so did FE_{NO} ($p = 0.002$) (Fig. 1). Comparing age groups revealed that changes in pulmonary function were significant in the adult but not pediatric cohort; this could possibly be related to relatively small sample sizes and the better pulmonary function among pediatric patients at baseline. In contrast, although FE_{NO} increased in all but one patient treated with ivacaftor, the effect on FE_{NO} was more pronounced in pediatric compared to adult patients (Fig. 1, Table 2). The median sweat chloride decreased from 86 to 37 mEq/l ($p = 0.0001$), independent of age.

Table 1
Baseline characteristics of ivacaftor study participants.

	Total (n = 15)	Adult (n = 8)	Pediatric (n = 7)
Age (years), mean ± SD	23.3 ± 16.2	36.3 ± 14.6	10.7 ± 3.8
Female/male	9/6	5/3	4/3
CFTR genotypes			
G551D/F508del	10	4	6
G551D/not found	2	2	–
G551D/2622+1G>A	1	–	1
G551D/E585X	1	1	–
G178R/F508del	1	1	–

CFTR, cystic fibrosis conductance regulator; SD, standard deviation.

Download English Version:

https://daneshyari.com/en/article/6240586

Download Persian Version:

https://daneshyari.com/article/6240586

Daneshyari.com