CHEST

Original Research

GENETIC AND DEVELOPMENTAL DISORDERS

Reduced Sodium Transport With Nasal Administration of the Prostasin Inhibitor Camostat in Subjects With Cystic Fibrosis

Steven M. Rowe, MD, MSPH; Ginger Reeves, CCRC; Heather Hathorne, CCRC; G. Martin Solomon, MD; Smita Abbi, PhD; Didier Renard, PhD; Ruth Lock, PhD; Ping Zhou, PhD; Henry Danahay, PhD; John P. Clancy, MD; and David A. Waltz, MD

Background: **Prostasin, a trypsin-like serine protease, is a channel-activating protease and major regulator of epithelial sodium channel-mediated sodium absorption. Its direct inhibition by camostat represents a potential approach to inhibiting sodium transport in cystic fibrosis (CF).**
Methods: **To determine whether a topical formulation of camostat represents an efficacious and tolerable approach to reducing Na+ transport in the CF airway, we conducted a two-part randomized, double-blind, placebo-controlled, crossover, ascending single-dose study to evaluate the pharmacodynamics, safety, and pharmacokinetics of camostat administered through a nasal spray pump in subjects with CF. Nasal potential difference (PD) was measured before and after treatment, and safety and pharmacokinetics were assessed by a standardized approach.**
Results: **In part 1, nine subjects were enrolled, and six completed crossover dosing at the maximally tolerated dose. The change in maximal (most polarizing) basal PD 2 h following administration of camostat was +13.1 mV (1.6-mg dose group) compared with −8.6 mV following placebo ($P < .005$). Intrasubject change in Ringer and amiloride-sensitive PDs exhibited similar and consistent responses. Bayesian analysis in an additional six subjects in part 2 estimated a dose of 18 μg/mL to provide 50% of the maximum effect. There was no significant change in chloride transport or total nasal symptom score, nasal examination rating, and laboratory parameters.**
Conclusions: **This study establishes the proof of concept that a reduction in sodium transport in the human CF airway can be achieved through inhibition of prostasin activity, identifying a potential therapeutic target in the disease.**
Trial registration: **ClinicalTrials.gov; No.: NCT00506792; URL: www.clinicaltrials.gov**

CHEST 2013; 144(1):200–207

Abbreviations: AE = adverse event; ASL = airway surface liquid; CAP = channel-activating protease; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane regulator; ENaC = epithelial sodium channel; NPD = nasal potential difference; PD = potential difference; SAE = serious adverse event

Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which functions as a chloride and bicarbonate channel in epithelial plasma membranes.[1] Normal CFTR function promotes anion and fluid secretion into the airway lumen, a process that is balanced by the absorption of sodium and fluid by the epithelial sodium channel (ENaC). In this model, an adequate volume of airway surface liquid (ASL) is maintained in the lungs to ensure effective mucociliary clearance. CF is characterized by abnormal ion transport in the epithelia of various organs, including the sweat glands and lungs. In the airway, impaired CFTR-mediated anion secretion limits mucosal hydration, thereby reducing the volume of ASL available to support effective mucociliary clearance.[2] Consequently, chronic airway infections and inflammation develop in patients with CF, resulting in a progressive loss of lung function.[3]

A number of investigational therapies are aimed at improving ASL volume and, thus, mucociliary clearance in CF. Apart from restoring CFTR directly through gene therapy or small molecule CFTR modulators to enhance epithelial fluid secretion, other potential therapies directed at increasing ASL volume include potent and selective ENaC inhibitors[4] and inhaled

hypertonic saline[5,6] and mannitol,[7,8] which enhance ASL volume by osmotic loading. Inhaled hypertonic saline also reduces the frequency of CF pulmonary exacerbations, improves quality of life,[6] and is widely used by patients with CF.[9]

Prostasin, a trypsin-like serine protease, is a major channel-activating protease (CAP) of ENaC-mediated sodium currents in CF epithelia.[10-14] Attenuation of ENaC function by CAP inhibition is predicted to improve mucociliary clearance with potential downstream effects on pulmonary obstruction and clinical stability. Camostat is an inhibitor of prostasin that has been shown to inhibit ENaC function in vitro[15] and in vivo.[16] An oral formulation of camostat has been marketed in Japan since the early 1980s to treat acute pancreatitis and postoperative reflux esophagitis through its antiprotease activity and has a reasonable safety profile. In this study, we tested an investigational formulation of camostat (QAU145) to determine the tolerability of topical administration and whether ENaC activity in patients with CF could be inhibited through this mechanism.

Materials and Methods

Study Population

Patients aged 18 to 50 years with CF (confirmed by clinical manifestations and evidence of CFTR dysfunction by sweat chloride and nasal potential difference [NPD] testing or by two known genetic mutations) were eligible for this study. Patients with a history of clinically significant ECG abnormalities, autonomic dysfunction, acute or chronic bronchospastic disease, allergies affecting the nasal or sinus passages, upper respiratory tract infection, any structural nasal abnormalities, history of immunodeficiency diseases, evidence of liver disease or injury, renal impairment, positive hepatitis B test results, or history of drug or alcohol abuse were excluded.

Study Design

This randomized, double-blind, placebo-controlled, alternating panel, ascending single-dose study was conducted in two parts as shown in Figure 1. Part 1 of the study comprised two panels (A and B) of three subjects each. In treatment periods 1 and 2, ascending single doses of camostat 0.2, 0.8, and 1.6 mg were administered. In treatment period 3, subjects received camostat 1.6 mg in a balanced crossover fashion with respect to treatment period 2. Different subjects within each panel were randomized to receive placebo in each treatment period. Each treatment period consisted of dose administration on day 1 and postdose evaluations up to 6 h postdose.

Part 2 of the study estimated the lowest efficacious dose of camostat. Six subjects completing period 3 in part 1 comprised part 2. Further details are provided in e-Appendix 1.

This study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. Approval was obtained from an independent institutional review board (Western Institutional Review Board, Olympia, WA; W20070738), and all subjects provided written informed consent before participating in the study.

Study Drug

Investigational camostat for nasal spray solution and placebo (lactose) were prepared by Novartis Pharma US and provided as lyophilized powder in vials. Both were reconstituted in 0.9% saline prior to administration.

Assessments

Nasal Potential Difference: The primary outcome was the change in maximal basal NPD from predose to 2 h postdose. The maximal basal NPD at predose and 2 h postdose was obtained as the maximum absolute value among measurements at 0.5, 1, 1.5, 2, and 3 cm in the target nostril. NPD is a validated model for proof of concept studies for ENaC inhibition in CF.[17-20]

In part 1, NPD was measured at baseline (day −1 of treatment period 1, ~24 h prior to dosing on day 1) in each nostril and at the end of the study as previously described.[18] In part 2, basal NPD was measured at predose in both nostrils for all subjects. At 2 h postdose, basal NPD was measured in the nontarget nostril, and a traditional NPD was performed in the target nostril.

A

Panel	Period 1		Period 2		Period 3	
			CROSSOVER			
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
A N=3 (A:P)	0.2 mg (2:1)		1.6 mg/MTD (2:1)		1.6 mg/MTD (1:2)	
B N=3 (A:P)		0.8 mg (2:1)		1.6 mg/MTD (2:1)		1.6 mg/MTD (1:2)

B

Subject number	Treatment Period 1	Treatment Period 2	Treatment Period 3
1	20 mcg	5 mcg	10 mcg
2	20 mcg	5 mcg	10 mcg
3	20 mcg	10 mcg	Placebo
4	Placebo	5 mcg	5 mcg

Figure 1. Study design, with randomization schemes for part 1 and part 2. A, Part 1 included two panels of subjects (three subjects per group) with repeat dosing and crossover design. B, Part 2 doses were determined using a Bayesian dose-response analysis and administered in the crossover design. A:P = active:placebo dosing ratio; MTD = maximally tolerated dose up to 1.6 mg.

Manuscript received October 2, 2012; revision accepted January 2, 2013.

Affiliations: From the Department of Medicine (Dr Rowe), Department of Pediatrics (Dr Rowe and Mss Reeves and Hathorne), Department of Physiology and Biophysics (Dr Rowe), and Cystic Fibrosis Research Center (Drs Rowe and Solomon and Mss Reeves and Hathorne), University of Alabama at Birmingham, Birmingham, AL; Novartis Institutes for BioMedical Research (Dr Abbi), East Hanover, NJ; Novartis Institutes for BioMedical Research (Dr Renard), Basel, Switzerland; Novartis Institutes for BioMedical Research (Drs Lock, Zhou, and Danahay), Horsham, England; Department of Pediatrics (Dr Clancy), Cincinnati Children's Hospital Medical Center, and University of Cincinnati, Cincinnati, OH; and Novartis Institutes for BioMedical Research (Dr Waltz), Cambridge, MA.

Funding/Support: This research was funded by Novartis Pharma US and supported by the National Institutes of Health [K23 DK075788 to Dr Rowe, P30 DK072482, and 5UL1 RR025777] and the Cystic Fibrosis Foundation [CLANCY09Y0 and CLANCY05Y2 to Dr Rowe].

Correspondence to: Steven M. Rowe, MD, MSPH, University of Alabama at Birmingham, MCLM 768, 1918 University Blvd, Birmingham, AL 35294-0006; e-mail: smrowe@uab.edu

DOI: 10.1378/chest.12-2431