Use Of Functional Respiratory Imaging (FRI) To Explore Drug Delivery And Lung Deposition Of Inhaled Liposomal Cyclosporine A (L-CsA-i) In Patients After Lung Transplantation

Benjamin Mignot[1], Cedric Van Holsbeke[1], Jens Paulukat[2], Amanda Copans[3], Noreen Roth Henig[4]
[1]FLUIDDA NV, Kontich, Belgium; [2]Breath Therapeutics GmbH, München, Germany;
[3]Former employee of Breath Therapeutics, a Zambon company, Menlo Park, CA, USA; [4]Kezar Life Sciences, South San Francisco, CA, USA

Introduction

Functional Respiratory Imaging (FRI)[1]

- FRI is a validated computational fluid dynamics (CFD)-based technique using aerosol delivery performance profiles, patients' high-resolution lung CT scans (HRCT) and realistic inhalation profiles to simulate aerosol lung deposition
- FRI provides quantifiable measures of drug performance, contributing to clinical proof of concept
- FRI-based biomarkers have been investigated as early indicators of bronchiolitis obliterans syndrome (BOS) in lung transplant patients

Bronchiolitis Obliterans Syndrome

- BOS is a progressive obstructive airway disease characterized by inflammation and fibrosis that results in respiratory failure and death[2]
- Currently there are no approved therapies for BOS

Liposomal cyclosporine A for inhalation (L-CsA-i)

- L-CsA-i is a novel proprietary liposomal formulation of cyclosporine A designed for inhaled delivery to the lungs administered via an Investigational eFlow® Technology nebulizer system (PARI Pharma GmbH)
- L-CsA-i is being evaluated for the treatment of BOS in patients following lung or allogeneic hematopoietic stem cell transplantation[3]

Study Objective

- The aim of this study was to characterize the airway deposition of L-CsA-i in lung transplant recipients with BOS using FRI

Methods

Subject Selection

- From a reference library of HRCTs, subjects who were bilateral lung transplant recipients and had two or more HRCTs from different timepoints were selected
- Twenty representative subjects without evidence of BOS at the first timepoint were identified; 10 subjects developed clinical characteristics and imaging consistent with the diagnosis of BOS while 10 did not
- Both groups were matched at baseline for age, height and FEV_1

FRI Computational Modeling

- In-silico three-dimensional models of the patient-specific conducting airways and lung lobes were extracted from the HRCT scans and converted to a computational domain
- L-CsA-i drug delivery parameters were incorporated to calculate aerosol airway deposition

Methods (cont'd)

Inhalation Profiles

- An optimized Investigational eFlow® Technology nebulizer system was used to administer L-CsA-i using continuous nebulization
- The profile is based on a tidal breathing of non-pathological lungs with a tidal volume of 500 mL, a respiratory rate of 12 breaths/minute and an inspiratory:expiratory ratio of 1:2 (Fig. 1)

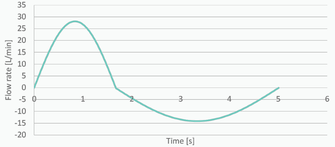


Figure 1. Breathing Profile

Particle Characteristics

- Aerosol characteristics of the eFlow® for L-CsA-i were evaluated, results from day 15 were used in this analysis (Table 1)
- The filling volume per dose was 2.5 mL L-CsA-i (10 mg dose)

Table 1. L-CsA-i Particle Characteristics[4]

Parameter	Day 1	Day 15	Day 30
Delivered Dose (%)	69.1 ± 6.2	69.7 ± 5.0	70.5 ± 2.0
MMAD (µm)	3.5 ± 0.0	3.5 ± 0.1	3.4 ± 0.1
GSD (--)	1.6 ± 0.0	1.6 ± 0.0	1.6 ± 0.0
FPF <5 µm (%)	76.5 ± 1.3	78.7 ± 0.8	81.0 ± 1.9
Nebulization Time	7.4 ± 0.4	8.9 ± 1.0	10.2 ± 1.4

Mass Median Aerodynamic Diameter (MMAD), Geometric Standard Deviation (GSD), Fine Particle Fraction (FPF)

Results

Patient Characteristics

- In those who developed BOS, mean age was 59.1 years, height was 172.6 cm, and FEV1 was 76.2 (%p) at baseline (t_0), compared to 58.6 years, 171.6 cm and 77.9 (%p) in those who did not develop BOS (Table 2)

Table 2. Characteristics of Those With and Without BOS

Did not develop BOS				
Gender	Age (y)	Height (cm)	FEV1 (L)	FEV1 (%p)
F	37.2	165.1	3.46	50.49
F	58.8	170.2	3.12	118.38
M	56.1	165.1	3.71	83.46
M	60.9	193.0	5.19	81.64
M	61.5	182.9	4.60	69.04
M	60.4	177.8	4.33	65.51
F	61.2	153.7	2.33	86.06
F	63.9	160.0	2.54	84.84
M	61.6	167.6	3.71	57.32
M	60.9	180.3	4.46	82.37
Average	58.3	171.6	3.74	77.91

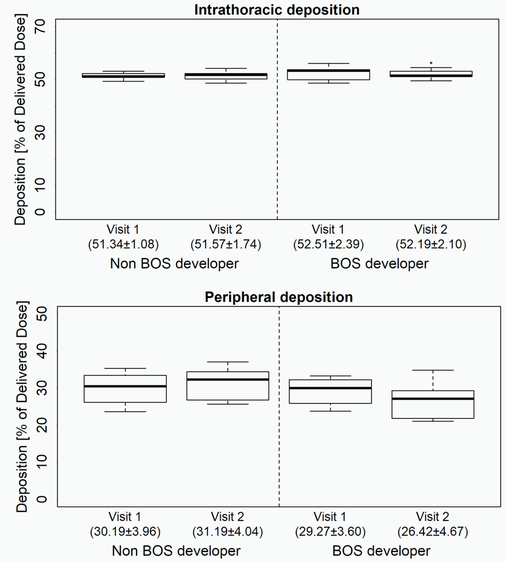
Developed BOS				
Gender	Age (y)	Height (cm)	FEV1 (L)	FEV1 (%p)
M	51.1	175.9	4.46	105.20
M	57.3	179.1	4.49	91.30
M	61.2	188.0	4.90	70.15
M	41.8	167.6	4.23	88.16
M	57.2	188.0	5.00	65.06
M	62.6	158.5	3.16	79.71
M	66.0	172.7	3.89	62.21
F	64.7	165.1	2.74	60.76
F	59.2	162.6	2.78	61.43
M	70.3	168.9	3.56	78.23
Average	59.1	172.6	3.92	76.22

Results (cont'd)

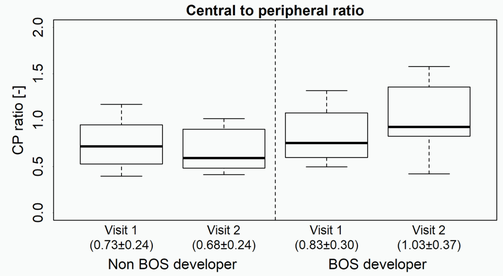
Deposition of Delivered Dose

- Intrathoracic deposition was similar at both time points in both BOS and non-BOS developers, with a mean and standard deviation of 51.90±1.88 percent of delivered dose (Fig. 2A)
- Of the deposited dose, patients who did not develop BOS had a slight increase in deposition to the peripheral airways, while the BOS group has a slight decrease in deposition to the peripheral airways (+1.00±2.68 versus -2.85±5.69 percent of delivered dose, Fig. 2B)
- A similar change was also seen in the central to peripheral ratio which went from 0.73±0.24 to 0.68±0.24 in the non-BOS and from 0.83±0.30 to 1.03±0.37 in the BOS groups, respectively (Fig. 2C)

Figure 2. Deposition of Delivered Dose: (A) Intrathoracic; (B) Peripheral; (C) Central to peripheral ratio



Results (cont'd)



Conclusions

- FRI has potential to become a useful biomarker for BOS patients
- FRI is useful to model aerosolized L-CsA-i deposition in BOS affected and unaffected airways
- FRI shows that L-CsA-i, a drug under development for the treatment of BOS, has >50% deposition when delivered via an optimized Investigational eFlow® Technology nebulizer system to target airways
- FRI also shows that L-CsA-i can reach affected airways at similar concentrations as unaffected airways

References

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- Benjamin Mignot and Cedric Van Holsbeke are employees of FLUIDDA
- Jens Paulukat is an employee of Breath Therapeutics, a Zambon company
- Amanda Copans is former consultant of Breath Therapeutics, a Zambon company
- Noreen Henig is former employee of Breath Therapeutics, a Zambon company

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