Liposomal Cyclosporine A for Inhalation (L-CsA-i): Innovation in the Treatment of Bronchiolitis Obliterans Syndrome (BOS)

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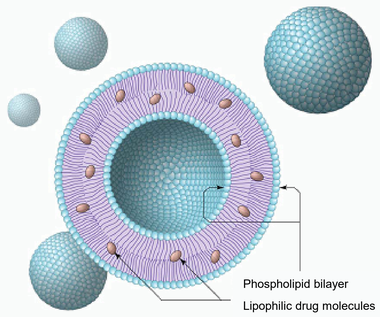
Introduction

- Bronchiolitis obliterans syndrome (BOS) is a fatal T-cell–mediated inflammatory lung disease commonly occurring after lung transplant[1] or allogeneic hematopoietic stem cell transplantation (alloHSCT)[2]
- BOS is an area in which there is unmet medical need. There are no approved therapies for BOS, and off-label use of oral therapies is limited by side effects and unproven efficacy[1]
  - Post-lung transplantation, the incidence of BOS is about 10% per year,[3] and half of these patients will die within 2.5 years of disease onset[4]
  - The incidence of BOS in alloHSCT patients is 8.3%[5]
- Cyclosporine is a potent anti-inflammatory agent that targets T cells.[6] When given systemically, however, it achieves low levels in the airways of the lungs,[7] and higher doses are associated with renal[6] and hepatic toxicity[8]
- Liposomal cyclosporine A for inhalation (L-CsA-i, **Figure 1**), a true liposome of cyclosporine A designed for inhaled delivery to the lungs via a customized nebulizer, may be a viable alternative
- A drug-specific Investigational eFlow® Technology nebulizer (PARI Pharma), optimized for L-CsA-i (eFlow for L-CsA-i), has been developed. This innovation in drug-device pairing is being evaluated for the treatment of BOS
  - Because BOS affects the small airways of the lungs,[1] particle size of the delivered drug is critical. Particle sizes of 1-5 µm are required to reach the small airways[9]
  - Additionally, treatment adherence may be impacted by use of the eFlow for L-CsA-i, depending on its ease of use as well as inhalation duration times

Purpose

- The purposes of the present experiments were to 1) determine the aerodynamic particle size distribution (APSD) of L-CsA-i, delivered dose of L-CsA-i, and inhalation time using the eFlow for L-CsA-i, and 2) evaluate the ease of use of the eFlow for L-CsA-i by the intended patient and healthcare provider populations

Figure 1. Liposomal Cyclosporine A (L-CsA-i). Lipophilic drug molecules are contained within the phospholipid bilayer. Lyophilized L-CsA-i, which is stable at room temperature, is dissolved in saline before use

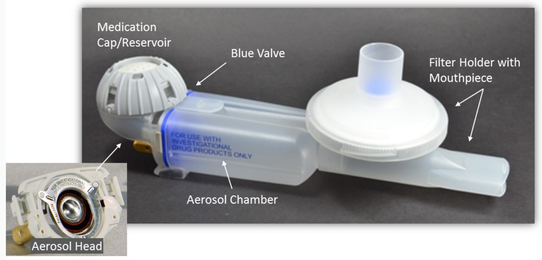


Methods

Simulated Use Test

- The eFlow for L-CsA-i (**Figure 2**) was studied in a simulated use test for reproducibility of aerosol delivery
- Five eFlow for L-CsA-i nebulizers were tested over the course of a month (Days 1, 15, and 30). Each nebulizer was tested once
- The simulated use test was conducted using the eFlow for L-CsA-i administering a 10-mg dose of L-CsA-i in a volume of 2.5 mL
- APSD and delivered dose were measured

Figure 2. The Investigational eFlow Technology nebulizer handset, optimized for liposomal cyclosporine A for inhalation. The eFlow technology nebulizes liquid drugs with a perforated vibrating membrane, generating an aerosol with a high percentage of droplets in a respirable size range



Human Factors Study

- The eFlow for L-CsA-i was assessed in a formative evaluation to determine whether the system could be used safely and effectively in the intended use environment with the intended patient and healthcare provider populations (**Figure 3**)
- This was a formative study, meant to assess influences on the process being developed as well as the successes of the operation at hand early in the device design process
- Tasks: Device assembly, drug preparation, treatment administration, cleaning, and troubleshooting
- Training: Healthy volunteers (N=6) had no prior training, lung transplant patients (N=5) were trained 6-12 hours ahead, and healthcare providers (N=5) were trained 1 week prior to the observation period

Figure 3. Demonstrated use of the Investigational eFlow® Technology nebulizer (PARI Pharma), optimized for liposomal cyclosporine A for inhalation. The eFlow® Technology nebulizer handset and eTrack Controller are shown

Results

Simulated Use Test

- Results for each of the testing days are presented in **Table 1**
- Overall mean values (averaged across days) are provided below:
  - Mean percentage dose delivered was 69.8%. L-CsA-i was aerosolized reproducibly with a mean mass median aerodynamic diameter (MMAD) of 3.5 µm
  - Mean fine particle fraction (<5 µm) was 78.7%
  - Mean drug delivery time was 8.8 minutes

Table 1. Mean Values of Delivered Dose, Mass Median Aerodynamic Diameter, Fine Particle Fraction, and Nebulization Time

Parameter	Day 1 Mean (SD) N=5	Day 15 Mean (SD) N=5	Day 30 Mean (SD) N=5	Change (%)
DD (%)	69.1 (6.2)	69.7 (5.0)	70.5 (2.0)	+2.1
MMAD (µm)	3.5 (0.0)	3.5 (0.1)	3.4 (0.1)	–4.7
FPF <5 µm (%)	76.5 (1.3)	78.7 (0.8)	81.0 (1.9)	+5.8
Nebulization time (min)	7.4 (0.4)	8.9 (1.0)	10.2 (1.4)	+37.8

Abbreviations: DD, delivered dose; FPF, fine particle fraction; MMAD, mass median aerodynamic diameter; SD, standard deviation

Human Factors Study

- Overall, the system was well received by participants
- Most procedural tasks could be carried out without error, and the majority of "pass with difficulty" rates could be explained through unfamiliarity of the system, forgetting training, or reliance on memory (rather than the use of the Instructions for Use [IFU] and Patient Information Leaflet [PIL]), and confusion over imagery/instructions in the draft IFU and PIL used in this study
- A final summative human factors study will be conducted
- A summative study collects data on outcomes hypothesized in a study and yields the effectiveness of the implementation program. In this case, the purpose being, for the updated device for commercial purpose along with updated instructions and training material, to demonstrate and confirm the ease of use in the intended patient population

Discussion

- Achieving adequate drug concentrations in the peripheral airways for the treatment of BOS requires the right combination of drug formulation and nebulizer system
- L-CsA-i particle size (measured as MMAD) delivered by the eFlow for L-CsA-i is approximately 3.5 µm, consistent with the ideal particle size for drug deposition in the small airways of the lungs,[9] which are most directly affected by BOS[1]
- The Human Factors Study showed that, despite the fact that training was done only once and in advance of the study (in some cases a week prior), all patients were able to successfully self-administer the treatment and use the device without major use errors
- L-CsA-i is currently in Phase 3 trials to evaluate its efficacy and safety for the treatment of BOS

Conclusions

- **L-CsA-i delivered via the eFlow for L-CsA-i resulted in production of aerosols in the ideal particle size range with efficient nebulization time and ease of use for patient and practitioner**
- **L-CsA-i has the potential to achieve high drug concentrations in the bronchioles with low systemic exposure**
- **A formative human factors study will provide input into the development of instructions for use and educational material**

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