New Inhaled Liposomal Cyclosporine A Formulation Gives Hope For Lung Transplant Recipients

Low-dose inhaled L-CsA formulation improves the pharmacologic profile, the highly variable bioavailability, and the severe side effects of oral CsA.

BY BOB BRUNO

According to the International Society of Heart and Lung Transplantation Registry, development of bronchiolitis obliterans (BO) is the single most important risk factor for five-year mortality among lung transplant patients. BO is a devastating, incurable disease of the small airways resulting in airflow obstruction. This disease affects approximately 60,000 patients worldwide. It is also a factor in other lung diseases such as collagen vascular diseases, inhalation of toxic fumes, and respiratory tract infections. Once the disease develops, a high number of patients die of respiratory failure within five years.

Lung Transplant Statistics

In 2006, more than 2,359 individuals were on the waiting list for lung transplants, and 115 were waiting for heart/lung transplants. In the United States, more than 1,400 lung transplants were performed, and more than 800 pediatric lung transplants were performed.

Lung transplantation is a treatment option for children and young adults with severe cystic fibrosis (CF), end-stage lung disease, and other chronic lung diseases. CF is the most common underlying disease that may require a lung transplant among children, adolescents, and young adults. Lung transplants are now performed at all ages — from newborn to adult.

It is unfortunate to note, however, that bronchiolitis obliterans syndrome (BOS) accounts for 30% of the deaths in lung transplant patients. By the fifth year after lung transplantation, 44% of the recipients who survived at least 14 days after transplantation developed BOS. The survival rate for patients who develop BOS is 20% to 40% lower than in patients without BOS.

A New And Promising Treatment

The June 2009 edition of the Journal of Aerosol Medicine and Pulmonary Drug Delivery features positive phase-1B clinical trial results for an inhaled liposomal cyclosporine A (L-CsA) for the prevention and treatment of BO.

Professor Jürgen Behr, head of the division of respiratory disease at the Ludwig Maximilians University, Klinikum Grosshadern in Munich, Germany, states: "PARI's (PARI Pharma, Munich, Germany) encouraging results show it is feasible and well tolerated to deposit relevant amounts of L-CsA into transplanted lungs. This has the potential to prevent and treat BO in a more efficient way compared with current oral standard treatment. Inhaled L-CsA has a favorable drug distribution to the target sites in the lung, which should lead to lower side effects than associated with systemic cyclosporine exposure."

About L-CsA

The body's immune system is designed to fight infections and treats newly transplanted organs such as the heart, liver, and lungs as "invaders." Cyclosporine (brand names: Gengraf, Neoral, Sandimmune) is an immunosuppressant and lowers the immune system's ability to fight infections.

The current standard treatment for lung transplant recipients is with oral cyclosporine A (CsA) which has severe side effects including kidney and brain damage, cancer, and vulnerability to infections.

It has been demonstrated that PARI Pharma's low-dose inhaled L-CsA formulation improves the pharmacologic profile, the highly variable bioavailability, and the severe side effects of oral CsA. The investigational proprietary liposomal formulation of 10 mg CsA/2.5 mL for inhalation is delivered via a customized Investigational eFlow Nebulizer System (PARI Pharma, Monterey, CA). The L-CsA formulation is based on an artificial lung surfactant carrier, is free of

any irritating organic solvents, and consists of unilamellar liposomes with an average diameter of 100 nm, where a nanometer is one-billionth of a meter. The unilamellar liposomes are obtained via a high-pressure homogenization process using standard pharmaceutical equipment (Microfluidics International Corporation, Newton, MA) followed by sterile filtration and lyophilization. It is important to note that the product has been successfully scaled up to production batch sizes, and preliminary stability data indicate that a shelf life of more than two years at room temperature is feasible.

"The long-term survival rate for lung transplant patients could be greatly improved through an effective inhaled liposomal cyclosporine therapy. Using our proprietary liposomal technology we created an inhaled formulation free from irritating solvents and optimized for administration via an Investigational eFlow Nebulizer System without destroying the liposome," stated Dr. Manfred Keller, executive vice president and chief scientific officer of PARI Pharma GmbH.

It is also important to note that in May of 2009, PARI received orphan drug designation from the Food and Drug Administration for its L-CsA, delivered via an Investigational eFlow Nebulizer System.

Benefits Of Inhalation Therapy

A principal benefit of inhalation therapy for a number of diseases (see figure 1) is the rapid onset of action, especially

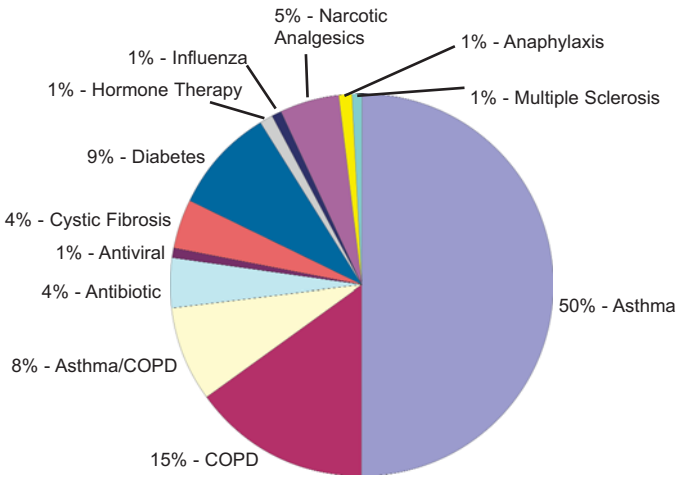

Figure 1: Disease class for inhalation drug delivery (courtesy of Ventaira Pharmaceuticals/Leslie Williams)

"The long-term survival rate for lung transplant patients could be greatly improved through an effective inhaled liposomal cyclosporine therapy..."

when compared to per orally ingested medicine (oral dosages). The fast medicinal action produced by inhalation delivery results from the large absorption area of the lung. For locally acting drugs, the onset of action is immediate. Systemically active inhaled drugs reach the blood stream quickly — within seconds. Rapid onset of action is especially important for rescue medications (i.e., asthma products), as well as pain medication and time-sensitive therapies, such as insulin. Patients cannot always afford to wait the 15 minutes or longer it often takes for a tablet to make its way though the gastrointestinal (GI) tract.

Avoiding the GI tract offers, through inhalation therapy, other advantages. Unlike per orally ingested medicine, inhaled drugs are not subjected to the first-pass metabolism effect that significantly reduces bioavailability. After a drug is swallowed, it is absorbed by the digestive system. The absorbed drug is then carried through the portal vein into the liver. Some drugs are so extensively metabolized by the liver that only a small amount of unaltered drug may enter systemic circulation. Further, stomach contents and variable absorption levels among patients add to the variability of bioavailability of the drug.

In addition to the problems of delayed onset of action and reduced bioavailability, per orally ingested medicines can also cause undesirable side effects in the GI tract. In contrast, medicines that are inhaled are better tolerated by the body, and delivery via the respiratory system provides a friendlier chemical environment less destructive to the medicine.

Injected drugs also avoid the problems associated with the GI tract, but needles are invasive by definition. In some instances, the social environment or physical constraints affecting the patient may make it difficult or socially uncomfortable to effect self-injection. Inhaled drugs are perceived as being more user-friendly than injections, resulting in better patient compliance for self-administered medications. Inhalation therapies also provide faster onset of action compared with intramuscular injection.

Effect Of Particle Size

The destination of aerosol particles is critical to the efficacy of inhalation therapy. For locally acting drugs, the particles obviously need to be deposited in the area of the respiratory tract requiring treatment. The treatment of asthma, for example, requires the inhaled drug reach the lower airways to achieve the desired therapeutic effect.

For systemically acting drugs, a high percentage of particles need to reach the alveoli deep in the periphery of the lung. The lungs contain about 300 million pulmonary alveoli that serve as the primary sites of gas exchange with the blood and are the fastest and most efficient area for absorption of systemically active drugs.

"The destination of aerosol particles is critical to the efficacy of inhalation therapy."

The extent of deposition of the inhaled particles (as opposed to the portion exhaled) and the location of the deposition depend largely on the size of the particles and the velocity of inspiratory flow.

Large particles in the range of 5-10 μm — where a micrometer, most commonly referred to as a "micron," is one-millionth of a meter — do not follow changes in the direction of airflow and have a tendency to be deposited by inertial impact; therefore, they tend to be deposited in the upper airways without reaching the site of action or reabsorption. Moreover, particles deposited in the mouth and throat can be swallowed and can lead to local or systemic side effects. This phenomenon is often observed with cortisone asthma medication, which can cause infections in the mouth.

Intermediate-sized particles (3-5 μm) can be carried further, into the bifurcations and smaller airways of the bronchi and bronchioles. Smaller particles (3 μm) behave more like gas molecules and follow the airflow all the way to the alveoli.

The smallest particles (0.5 μm) can fail to be deposited in the alveoli, and portions of the medicine can resultantly be exhaled, therefore not achieving the desired therapeutic levels. Controlling the air velocity by slow inhalation will maximize the number of particles that reach the alveoli and minimize the number exhaled.

Formulations

The size of the aerosol particle entering the body is a function of the inhaler device and the formulation of the medication. Inhalers and nebulizers of different types each have the ability to generate aerosol particles of certain size range.

For liquid formulations containing soluble drugs, the size of the aerosol particle is largely a function of the design and operation of the delivery device such as a nebulizer or "atomizer" that converts the liquid into a vapor or mist.

However, for drugs in powder form and for insoluble drugs suspended or dispersed in emulsions, the particle size in the formulation of the drug product is critical. The formulation of the drug product and the design of the delivery device must be matched in order to produce uniform and optimally sized aerosol particles.

For example, if a pharmaceutical company is formulating liquid medication with suspended drugs, and the goal is to deliver aerosol droplets with a mean particle size of 3.0 μm, the component drug suspended inside the liquid droplets must have a particle size smaller than 3.0 μm. Otherwise, the droplet would not be able to carry the drug and would remain "empty." Therefore, when formulating liquid inhalation medication with suspended drugs, the size distribution of particles must be carefully adjusted and controlled.

The actual size of the drug particle depends on the type of dispersed system (suspension, emulsion, liposome, or colloidal system). Studies performed clearly indicate that the inhalation efficiency with suspended drug particles will dramatically increase when the drug size falls below 1.0 μm.

It may be noted that aerosol droplets are typically not uniform in size but rather have a size distribution. In other words, an aerosol with a mean particle size of 3.0 μm will contain some particles larger and smaller than the mean size.

A goal of inhalation therapy researchers is to continue their work to create drug formulations with uniform particle size distributions, most often depicted as bell curve graphs.

Bob Bruno *is an established freelance writer with more than four decades of experience in corporate management, marketing, and sales and engineering. Until his retirement in 2008, he was president and COO of Microfluidics International Corp. for seven years and VP of marketing and sales the five previous years. In prior years, he was VP of marketing and sales at Azonix Corp. and VP and general manager at Inframetrics Inc., which is now FLIR Systems Inc. Early in his career he was senior aerospace engineer at Honeywell Radiation Center and at RCA. He holds B.S.M.E. and M.S. degrees in Mechanical Engineering from Northeastern University.*