BALANCING ACT

BY ERIN MCCALLISTER, SENIOR EDITOR

Newly marketed drugs for cystic fibrosis and much of the CF pipeline focus on correcting the mechanisms responsible for aberrant mucus buildup in the airways, but mucus is only half the problem. Laurent Pharmaceuticals Inc. hopes to tackle the other half of the problem with LAU-7b, an oral formulation of fenretinide that could correct the inflammatory imbalance in CF patients.

The company believes the compound could reduce lung deterioration over time, when given on top of SOC.

“The innate immune-inflammatory response is also affected in the CF lung, independent from the mucus defect, as there is evidence of up-regulation of inflammation in newborns in the absence of mucus plugging and in the absence of infection,” said President and CEO Radu Pislariu.

CF patients have low concentrations of docosahexaenoic acid (DHA) and high concentrations of arachidonic acid (AA), which are fatty acid components of the key inflammatory mediators docosanooids and eicosanoids, respectively.

Pislariu noted that high levels of arachidonic acid may increase pro-inflammatory factors and stimulate mucus secretion, while the deficiency of DHA may explain why CF patients have an exaggerated and unresolved inflammatory response and are unable to fight opportunistic infections such as Pseudomonas aeruginosa.

While fenretinide’s exact mechanism in CF is unknown, researchers at McGill University showed that in macrophage cell lines, the synthetic retinoid acts via the ERK pathway to correct the DHA/AA imbalance and inhibit macrophage inflammatory mediators.

In June, Laurent announced results from a Phase Ib study of LAU-7b, which appeared to confirm these effects. According to ClinicalTrials.gov, the primary aim of the study was to assess the safety and tolerability of LAU-7b, with measurements of plasma arachidonic acid and DHA as secondary endpoints, along with several inflammatory biomarkers. Pulmonary function was assessed using FEV1, and the study also measured quality of life.

In the placebo-controlled trial in 15 adult CF patients, LAU-7b normalized lipid imbalance and reduced oxidative stress “in the vast majority” of patients, causing a shift toward an anti-inflammatory pattern, the company said.

The trial tested three ascending doses of LAU-7b over 21 days. Patients had to be stable on available CF therapies, meaning no exacerbations in the last 30 days. Additionally patients had to have chronic pulmonary P. aeruginosa infection.

In animal models, LAU-7b had shown a positive effect on P. aeruginosa infection and the company had considered testing this hypothesis as part of the Phase Ib study. However, it would have required an induced sputum analysis, “which is an aggressive procedure” for a Phase Ib study where the primary aim is to assess the candidate’s safety. “We dropped the outcome measurement on sputum, for ethical reasons, but the P. aeruginosa criteria was kept,” Pislariu said.

Detailed results from the trial were not disclosed.

Laurent hopes that by getting the inflammatory response in check, LAU-7b could decrease the rate of lung deterioration over time.

“The development of such treatments could prevent the initiation of the inflammation-infection vicious cycle and the consequent lung damage, which is the most frequent cause of mortality in CF,” Pislariu said.

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RADU PISLARIU, LAURENT PHARMACEUTICALS

The biotech hasn’t said what endpoints it plans to measure in future studies of LAU-7b to show an effect on lung deterioration, but the company expects that LAU-7b would be given on top of available therapies for CF, including new drugs like Kalydeco ivacaftor and Orkambi ivacaftor/lumacaftor from Vertex Pharmaceuticals Inc.

Kalydeco is a small molecule potentiator of CF transmembrane conductance regulator (CFTR), and lumacaftor is a small molecule CFTR conformational stabilizer. Both help to restore function of the CFTR and reduce mucosal buildup; however, there are no published data on the effect of the drugs on inflammatory biomarkers. Vertex did not respond in time for publication to questions regarding whether or not it has seen any effect.

Fenretinide is an old molecule that has been tested in several other indications, including ophthalmic diseases and cancer. But Pislariu notes that LAU-7b works via a different mechanism in CF than what is being tested in these other diseases.

In addition, Laurent has developed a novel, solid dosage powder formulation that overcomes a problem with using previous formulations in CF patients. Namely, previous formulations of
fenretinide used a corn oil-based suspension, and CF patients have problems absorbing oil-based compounds and typically require much higher doses.

Pislariu said that the Phase Ib results showed that Laurent was able to achieve “the targeted pharmacokinetic profile desired in adult CF patients.”

Laurent has exclusive, worldwide rights from McGill to method of use patents for fenretinide, which include its use in CF.

COMPANIES AND INSTITUTIONS MENTIONED
Laurent Pharmaceuticals Inc., Montreal, Quebec
McGill University, Montreal, Quebec
Vertex Pharmaceuticals Inc. (NASDAQ:VRTX), Boston, Mass.

REFERENCES