European Cystic Fibrosis Society

Journal of Cystic Fibrosis
The Official Journal of the European Cystic Fibrosis Society

Cystic Fibrosis Research News

Title:

PREDICTIVE FACTORS FOR LUMACAFTOR/IVACAFTOR CLINICAL RESPONSE

Authors:

Alexandra Masson[a,b], Elena K. Schneider-Futschik[c,d], Nesrine Baatallah[e], Thao Nguyen-Khoa[a,e,f], Emmanuelle Girodon[e,g], Aurélie Hatton[e], Thomas Flament[h], Muriel Le Bourgeois[a], Frederique Chedevergne[a], Céline Bailly[a], Sylvia Kyrilli[a], Diane Achimastos[a], Alexandre Hinzpeter[e], Aleksander Edelman[e], Isabelle Sermet-Gaudelus[a,e,i]

Affiliations:

[a]Centre Maladie Rare Mucoviscidose. Hôpital Necker-Enfants Malades, Assistance-Publique Hôpitaux de Paris, 149 rue de sèvres, 75015 Paris, France.
[b]Centre de Référence et de Compétence de la Mucoviscidose. Hôpital Dupuytren, 8 avenue Dominique Larrey, 87042 Limoges, France.
[c]Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmacy and Pharmaceutical Sciences. Monash University, Parkville, Victoria, 3052, Australia.
[d]Lung Health Research Center, Department of Pharmacology & Therapeutics, School of Biomedical Sciences, Faculty of Medicine, Dentistry and Health Sciences. The University of Melbourne, Parkville, VIC, Australia.
[e]Institut Necker-Enfants Malades. INSERM U1151, 149 rue de Sèvres, 75015 Paris, France.
[f]Laboratoire de Biochimie Générale. Hôpital Necker-Enfants Malades, Assistance-Publique Hôpitaux de Paris, 149 rue de Sèvres, 75015 Paris, France.
[g]Service de Biochimie et Génétique Moléculaire. Hôpital Cochin, Assistance-Publique Hôpitaux de Paris, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France.
[h]Centre de Ressources et de Compétence de la Mucoviscidose Adulte, Hôpital Bretonneau, Centre Hospitalier Régional Universitaire, 2 boulevard Tonnellé, 37000 Tours, France
[i]Université Paris Sorbonne. 75005 Paris, France.

What was your research question?

Which are the factors involved in the variability of the response to Orkambi?

Why is this important?

Ivacaftor-lumacaftor (Orkambi®) combination therapy improves disease symptoms (clinical status) of people with Cystic Fibrosis (CF) with two F508 del mutations but the clinical response is highly variable. It is of the utmost importance to better understand the reason of this variability.

European Cystic Fibrosis Society

Journal of Cystic Fibrosis
The Official Journal of the European Cystic Fibrosis Society

Cystic Fibrosis Research News

What did you do?

Patients aged 12 years or over took part before starting Orkambi® in a study at Necker Enfants Malades Hospital, Paris. Additional to the routine evaluation of height and weight (expressed in Body Mass Index (BMI)), increased of infection (exacerbations), presence of bacteria in sputum, adherence to treatment, lung function tests (Forced Expiratory volume in one second (FEV_1)), and sweat test, patients also could agree to undergo several tests conducted at the initial visit and 6 months. These included: blood samples (to measure lumacftor/ivacaftor blood concentration); genetic analysis of the *CFTR* gene (to search for other mutations in addition to the F508del mutation which might modify the response to Orkambi®); measurements of CFTR function in sweat , the nose (nasal potential difference (NPD)), or in the rectal tissue (biopsy for intestinal short-circuit (Isc) current measurements (ICM)).

What did you find?

Forty-one patients started but treatment was stopped in 5 patients before the 6 months follow-up, as a result of either poor tolerance (2 patients) or poor intake of the drugs (3 patients). At 6 months of treatment, FEV_1 had increased significantly by 5%, as well as BMI by 3.7%, but the number of antibiotic courses and the bacteria in the airways were not significantly changed. The mean amount of air that remains in the lungs after maximally breathing out (Residual Volume (RV)), , was normalized at 6 months.

CFTR activity also improved but this did not reach the significant level in all the tissues tested. The tests for CFTR function showed absence of activity before Orkambi® initiation. A significant decrease$^-$ was observed for the sweat test whereas the β-adrenergic sweat secretion rate did not vary in the 9 patients who underwent these tests. The average level of F508del-CFTR activity at 6 months significantly increased to 15% of the normal level in the rectal tissue (ICM was tested in 12 patients) and to 20% in the nose (NPD was tested in 21 patients) but this latter test did not reach a significant level because of a high variability. Changes at 6 months in FEV_1 or BMI had no relation with the change in CFTR activity nor to drug levels in the blood. Interestingly, improvement in ICM was related to improvement in lung volume after breathing out maximally RV. Additional mutations in the *CFTR* gene were seen in 4 patients. One of those abolished the lumacaftor corrector effect.

What does this mean and reasons for caution?

This thorough evaluation shows that (i) biomarkers of CFTR activity, assessing the Chloride transport, have no relation with the improvements in disease symptoms at 6 months at an

individual level; (ii) lumacaftor and ivacaftor blood levels are not predictive of the effects on the disease (clinical response) in this small patient group; (iii) additional genetic variants may influence CFTR correction and must be investigated.

What's next?

Other markers of CFTR activity must be looked at such as bicarbonate transport (an acid controller) or inflammation. It is very important to search additional variant of the CFTR gene while treating the patients with CFTR modulators.

Original manuscript citation in PubMed

https://www.ncbi.nlm.nih.gov/pubmed/?term=PREDICTIVE+FACTORS+FOR+LUMACAFTOR%2FIVACAFTOR+CLINICAL+RESPONSE