

Cystic fibrosis: the therapeutic revolution of CFTR channel function restoring drugs

Press release of the French National Academy of Medicine (*¹)

October 5, 2021

Cystic fibrosis is an autosomal recessive genetic disease, whose prevalence is 1/3000 births in Europe, and which affects many organs: lungs, pancreas, liver, intestines, skin, urogenital system, and others (1). It is a chronic disease responsible for a significant impairment of quality of life, despite nutritional support, pancreatic extracts, multi-daily respiratory physiotherapy and repeated courses of antibiotics. Systematic neonatal screening, non-specific treatments and multidisciplinary care in the 47 resource and competence centers in France have made it possible to increase life expectancy at birth beyond 35 years. Despite lung and even multi-organ transplants, the disease is still the cause of sometimes early mortality (2).

A gene encoding a protein required for *Cystic Fibrosis Transmembrane Regulator* (CFTR) activity, present in ion channels, has been discovered. This protein allows the epithelial excretion of chlorine and bicarbonate ions and secretion of fluid mucus (3). Mutation of this gene causes cystic fibrosis by the absence or deficiency of this protein. More than 2 000 mutations have been described, classified from I to VI according to the type of CFTR protein deficiency (4). The clinical impact is determined by the class of mutations and the presence of one or two identical alleles. It is severe in the case of the *F508del* mutation, characterized by an absent CFTR activity (>80% of French patients), or in one of the rare mutations characterized by a residual CFTR activity. Various CFTR channel function restorers have been developed and tested in clinical trials versus placebo,

(*¹) Press release from the Academy's Rapid Communication Platform validated by the members of the Board on October 4, 2021.

first in patients over 12 years, then in children aged 6 months to 11 years, while the pharmacodynamics and safety of these molecules were verified between the ages of 6 months to 5 years and 4 to 6 months (5).

The first function restorer tested was a potentiator of residual CFTR function: ivacaftor (Kalydeco®) (6). Then, combinations of a potentiator and strictly speaking restorers of CFTR function in patients homozygous for the *F508del* mutation (characterized by the absence of CFTR protein) or heterozygous (*F508del*/mutation with residual activity), such as lumacaftor + ivacaftor (Orkambi®) (7) or tezacaftor + ivacaftor (Symkevi®) (8) have been tested. Finally, a triple combination of ivacaftor + tezacaftor + elexacaftor (Kaftrio®) has shown an excellent efficacy in patients homozygous for the *F508del* deletion on the reduction of sweat chloride, improvement of respiratory function (FEV1), reduction in annual pulmonary disorder exacerbations and antibiotic consumption (9,10).

Kaftrio® has recently received a marketing authorization in France for patients with the *F508del* mutation. Other mutations are likely to respond, depending on the results of the study of the cells that have been collected from the patients in order to choose the best treatment option (11).

It is encouraging to hear from patients that their quality of life has significantly improved and to note that the number of annual lung transplants for cystic fibrosis has decreased in France from 72-80 to 33 (-57%) between 2018 and 2020, without increased deaths in the absence of transplantation (11).

The French National Academy of Medicine considered it important to make known these major therapeutic advances in the fight against cystic fibrosis. It emphasizes that:

- The diagnostic and therapeutic perspectives opened up in cystic fibrosis make it possible to consider a real strategy of personalized medicine;
- The prognosis of this disease is likely to improve significantly if these new treatments demonstrate, on the long term, the maintenance of their effectiveness on survival and quality of life, as well as their tolerance.

References

- (1) Shteinberg M, et al. Lancet 2021; 397:2195-211.
- (2) www.registredelamuco.org
- (3) Kerem B, et al. Science 1989; 245:1073-80.
- (4) Zielenski J, et al. Annu Rev Genet 1995; 29:777-807

- (5) <https://www.cff.org/Trials/Pipeline>
- (6) Ramsey BW, et al. *N Engl J Med* 2011; 365(18):1663-72.
- (7) Wainwright CE, et al. *N Engl J Med* 2015; 373(3):220-31.
- (8) Taylor-Cousar JL, et al. *N Engl J Med* 2017; 377(21):2013-23.
- (9) Middleton PG, et al. *N Engl J Med* 2019; 391(19):1809-19.
- (10) Heijerman HGM, et al. *Lancet* 2019; 394:1940-8.
- (11) Pranke I, et al. *Am J Respir Crit Care Med* 2019; 199(1):123-126.
- (12) Burgel PR, et al. *Am J Respir Crit Care Med* 2021; 204(1):64-73