Evolution of diagnosis and treatments for cystic fibrosis of pulmonary involvement: a transition from broad spectrum drugs to target drugs. A critical review

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Introduction

Cystic fibrosis (CF) is the genetic disease with the highest incidence in the Caucasian population with a rate of 1: 3500 live births (Farrell 2008). Although it has always been a pediatric disease, this disorder has a higher incidence in adults due to the increase in life expectancy of patients thanks to the design of target drugs that treat specific mutations of the Cystic fibrosis transmembrane conductance regulator (CFTR) gene. The defective mucociliary action of this disease and the accumulation of hyperconcentrated secretions clogs the airflow of the airways and inhibits the proper activation of antibacterial defensins, facilitating the microbial colonization of the respiratory tract, causing repeated infections with progressive loss of pulmonary function. At present, its current treatment is palliative, controlling lung damage, and there is a need to find a curative treatment with which patients do not see their life conditioned by the disease.

Diagnosis (Rosentein & Cutting 1998)

Conventional methods:

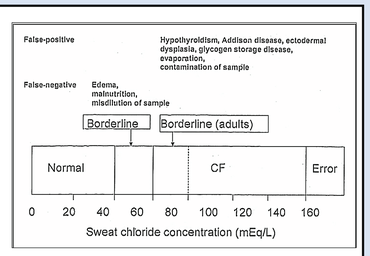
- *Sweat test*: measurement of chloride concentration in sweat after iontophoresis of pilocarpine. A sweat chloride concentration of more than 60 mmol/L is consistent with the diagnosis of CF.

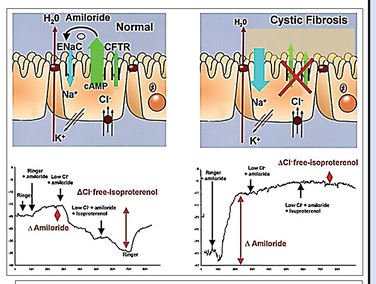
- *Transepithelial nasal potential difference*: Three features distinguish CF: (1) higher (raised) basal PD, which reflects enhanced Na+ transport across a relatively Cl−-impermeable barrier; (2) greater inhibition of PD after nasal perfusion with the Na+ channel inhibitor, amiloride, which reflects inhibition of accelerated Na+ transport; and (3) little or no change in PD in response to perfusion of the nasal epithelial surface with a Cl−-free solution in conjunction with isoproterenol, which reflects an absence of CFTR-mediated Cl− secretion.

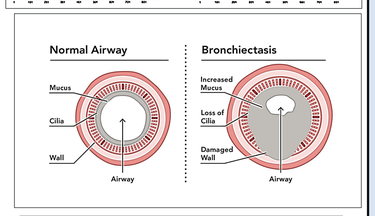
- *Radiological criteria*: appearance of bronchiectasis, which facilitate microbial colonization, which results in a loss of lung function.

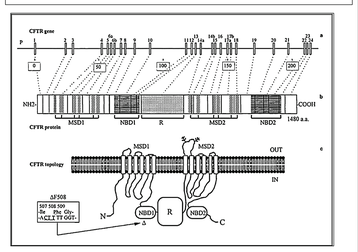
Molecular methods:

- *CFTR gene screening*: screening for the different mutations to identify molecular defects causing CF.



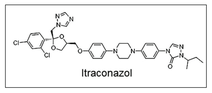


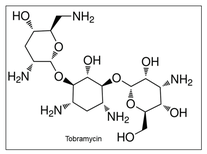


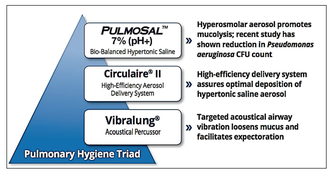


Treatments

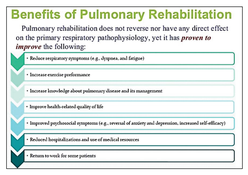
- *Antibiotics, Antifungals & Mucolytics*: to control chronic pulmonary recurrences of the disease (*Aspergillus fumigatus* & *Pseudomona aeruginosa* mainly), and facilitate expectoration (hyprtonic saline).



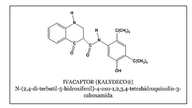




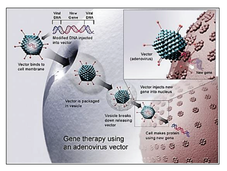
- *Respiratory physiotherapy*: to remove accumulated mucus in the respiratory tract.



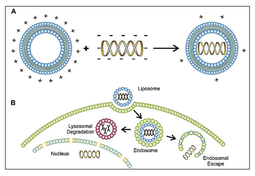
- *Target drugs*: personalized medicine. They correct certain molecular alterations. They can not be applied to all patients, they are medicines directed to specific people (e. g. ivacaftor).



- *Gene Therapy*: under investigation. It would reverse alveolar damage and resume altered cellular processes (virus or plasmids as vectors to insert a correct CFTR gene into host´s DNA.



Virus



Plasmids

Discussion and Conclusion

Patients with cystic fibrosis who reach adulthood are facing a limit medical situation. The existing treatments to date, including the target drugs, present a palliative character increasing the hope and quality of life of the individual. However there is a tipping point in which the respiratory function declines compromising the life of the patient. Because of this it is extremely important to make research advances that envolve a curative therapy, such as the application of a gene therapy that, by inserting a functional copy of the CFTR gene into the patient's DNA, allows the correct resumption of all the altered cellular processes, thus resuming a correct mucociliary function of the respiratory epithelium and regenerating the alveolar damage (Rodríguez Sousa 2018). It is in this line where future research should focus in order to be able to completely reverse the effects of cystic fibrosis in the future.

References

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