New treatments in Cystic Fibrosis

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Cystic Fibrosis (CF) is the most common life-limiting autosomal recessive disease in Caucasians[1]. It is a multisystem disease that is mainly characterized by respiratory and gastro-intestinal manifestations. CF affects 1 in 3500 live births in Caucasians but is much rarer in other populations[2] whereas about 1 in 20 to 1 in 37 individuals are healthy carriers of the recessive gene[3]. Accurate data are lacking in Greece, however it is estimated that the number of patients is around 1000. The median age of death in the annual USA and European reports is below 30 years[4,5]. Due to the continuous and significant increase in survival, even though some decades ago CF patients did not reach adulthood, today about half of the CF population are adults[6]. The main cause of death in over 70% is respiratory failure[4], however CF is not widely known to chest physicians who still consider it as a children's disease and that may interfere with its optimum management.

CF is caused by mutations of a gene located on the long arm of chromosome 7 which encodes a 1,480 amino-acid protein. This protein is known as the cystic fibrosis conductance regulator (CFTR) and operates as a chloride and bicarbonate channel on the apical membrane of epithelial cells[1]. The defective function of the CFTR gene leads to an abnormal conductance of the chloride channel which is regulated by cAMP. It is noteworthy that 2000 different mutations of the CFTR gene have been discovered so far some of which have an unknown impact[7,8], and this number along with the effect of other genes lead to the different phenotypes of the disease. Mutations of the CFTR gene can be divided into 6 classes[2,9]:

I. Total absence of CFTR synthesis
II. Defective CFTR maturation and transportation to the cell surface
III. Defective reaction and regulation of the protein- the open probability is reduced
IV. Reduced channel conductance due to abnormal CFTR
V. Reduced transcription due to abnormal conjunction to the endoplasmic reticulum resulting in reduced number of channels on the cell surface
VI. Reduced stay of the channel on the cell surface.

As the CFTR mutation penetration is limited, the genotype cannot fully predict disease severity which is also regulated by other mutations and epithelial Na+ channel function (eNAC)[10].

In the vast majority of patients which reaches 87.2% in Europe, CF is caused by class II mutations[11]. The relative frequency of the CFTR mutations varies between countries. The commonest mutation is Phe508del, which belongs in class II. The percentage of Phe508del in the alleles of different

European countries ranges from 23.77% in Israel to 81.97% in Denmark[5] and is higher in Northern and Central Europe than in Southern Europe. It is estimated that a very high percentage of CF patients worldwide (up to 45%) are homozygous for this allele[12]. In addition a rarer class III mutation, G551D is quite common in Ireland (8.47%) but rare in Scandinavian countries and Southern Europe. In Greece, the percentage of Phe508del homozygotes is relatively low, about 28%[5]. Furthermore, Greece ranks first in the frequency of 3 out of the 15 commonest mutations in Europe[5]. These two facts render our country quite unique in the distribution of different mutations and that has consequences in the management of the disease, as described below.

The discovery of the CFTR gene in 1989[13] raised hope for the definite cure of the disease by gene therapy which is based on the introduction of the normal CFTR gene by a vector into the abnormal CF epithelial cells[2]. Gene therapy would obviously have two basic advantages: dealing with the root of the disease and being effective in all patients irrespective of their mutation. However it soon became apparent that the route to CF cure was more difficult than initially anticipated. Gene therapy did not turn out to be as easy as once thought due to a number of reasons including the ability of the respiratory epithelium to keep out foreign genetic material, the presence of viral vector receptors on the basolateral but not the apical membrane (where the CFTR is located) and the presence of antibodies[2,14,15].

The current management of CF is situated on the opposite side of gene therapy and consists of management of symptoms. It includes enzyme replacement therapy, inhaled mucolytic and hyperosmolar solutions, antibiotics administered both systematically and by inhalation, airway clearance techniques, nutritional support and bronchodilators[16]. This multidisciplinary approach in the setting of organized CF centers has literally changed the natural course of the disease. This change is clearly indicated by the median predicted survival, which is the age that 50% of patients is expected to reach in a certain year. Based on the USA CF Foundation, median predicted survival was 28 years in the period 1986-1990 and 39 years in the period 2010-2014[4]. In addition the median age of death increased by 3 years in the last 15 years (4=CFF). Based on these facts it is realistic to assume that children with CF born today may actually reach the 5th-6th decade[17]. However current treatments are time-consuming, rendering the every-day life of CF patients extremely difficult while survival is still heavily compromised.

In the recent years a new category of drugs called CFTR modulators have been introduced, thereby opening a new era in the treatment of CF. Modulators are aiming at the abnormal protein in contradiction to gene therapy which aims at the abnormal gene and current treatment which is dealing with CF symptoms[1,2,18]. In this setting treatment is individualized according to the CFTR defect, and the underlying mutation. Three new subcategories of *per os* drugs have been studied in this direction and involve the first 3 mutation classes:

1. Agents that promote ribosomal readthrough of nonsense mutations, such as ataluren
2. CFTR correctors which improve CFTR trafficking to the cell surface and its function, such as lumacaftor
3. CFTR potentiators which increase time of the open state of the channel that is already situated on the cell surface, such as ivacaftor[1,2].

Ivacaftor, the first modulator that has been approved was considered the most important new drug of 2012[2]. The initial phase II study[19] showed improvement of lung function and of chloride transport both by nasal potential difference and sweat chloride concentration in patients with at least one copy of the G551D mutation. The results were confirmed by two phase III studies. STRIVE[20] in patients above 12 years of age with an FEV_1 40-90% and ENVISION[21] in patients over 6 years old with an FEV_1 40-105% showed that in patients with at least one G551D allele ivacaftor resulted in improvement of sweat chloride concentration and pulmonary function within two weeks and also increase in body weight, improvement of quality of life and reduction of exacerbations. These results are sustained after prolonged use so that longer term effects become apparent, i.e. less frequent infection with *P. aeruginosa*, decrease in lung function decline, improvement in glucose tolerance and in growth in children[22,23].

Unfortunately ivacaftor is effective in a minority of patients. G551D is the most common class III mutation affecting 4% of patients[24], whereas this percentage is even lower in Greece. In this mutation class the channel is located on the cell surface and with ivacaftor the time it is open increases resulting in adequate chloride transport. Ivacaftor is also indicated for other rarer class III mutations and one class IV mutation, R117H[18,25]. However administration of ivacaftor in Phe508del homozygous patients did not have positive results (DISCOVER[26]). This observation was rather anticipated since in this case folding and processing of the abnormal protein to the cell surface is problematic whereas ivacaftor improves channel function when it is already in its proper location.

Therefore only 7% of CF patients can actually benefit from ivacaftor and the percentage is lower in Greece[18].

The attempt to restore channel processing to the cell surface in homozygous Phe508del patients led to lumacaftor, a corrector that in vitro improves Phe508del CFTR function. In the initial phase IIa study lumacaftor resulted in a decrease of sweat chloride values but not in improvement of nasal potential difference or lung function[27]. Consequently a phase II study of co-administration of lumacaftor/ ivacaftor in homozygous or heterozygous Phe508del patients was designed in order to estimate the benefit of combined treatment[28]. A small but significant increase in FEV_1 in homozygotes but not heterozygotes was observed. It should however be noted that the number of heterozygotes was small (27 patietns) and different mutations were included. In any case this study was considered a mile stone in CF treatment as it showed that management of the basic defect in the most common CF mutation was possible.

As a consequence two phase III studies, TRANSPORT and TRAFFIC were performed with moderate results. After 24 weeks of lumacaftor/ ivacaftor in 1108 homozygous Phe508del patients over 12 years of age with mean FEV_1 61%[29] an improvement of FEV_1 by 2.6-4% (primary endpoint) was observed. This small increase was observed in all patient groups regardless of age, lung disease severity, gender and chronic *P. aeruginosa* infection. In addition exacerbation rate was reduced by 30-39% and BMI improved. Lumacaftor/ ivacaftor was well tolerated and rate of discontinuation due to an adverse event was 4.2% among patients who received the drugs versus 1.6% among those who received placebo.

Although improvement of pulmonary function in TRANSPORT and TRAFFIC was statistically significant, it was so small that its clinical relevance is doubtful. However reduction of exacerbation rate and BMI increase were considered adequate and the lumacaftor/ivacaftor combination was approved by the FDA on July 2nd, 2015 for homozygous Phe508del patients over 12 years of age. Therefore the first modulator treatment for almost half the CF population worldwide is now available[18]. However the high cost of this treatment (around 300.000 dollars per year) raises important considerations regarding its availability[30]. In any case, approval of the lumacaftor/ ivacaftor combination opens a new era in CF treatment and several clinical studies with other correctors and potentiators are underway for homozygous and heterozygous Phe508del patients[18].

Regarding CFTR class I mutations which affect about 10% of the CF population approval of another modulator is not far away[1,2]. In class I mutations, protein synthesis is terminated before it reaches its full length, due to a premature termination codon in mRNA. The first drugs used for this class were aminoglycosides (31=ισπ 18). However, toxicity and parenteral way of administration contributed to an unfavorable profile, while benefits were not universal[32,33]. A synthetic alternative is ataluren which has already been approved for patients with Duchenne muscular dystrophy due to a stop codon[2,34]. After phase II studies according to which ataluren was proven safe and well tolerated[35-38], a phase III study was published in 2014[39]. This study included 238 patients with at least one class I mutation, aged over 6 years. No significant difference in pulmonary function or exacerbation rate between ataluren and placebo was observed. Nevertheless, in the subgroup not receiving inhaled tobramycin a statistically significant improvement of the above parameters was detected. The authors hypothesized that tobramycin may interfere with ataluren's mechanism of action thus ataluren without co-administration of tobramycin is currently being studied in a new phase III study.

Introduction of modulators in the treatment of CF is a significant step forward for all inherited diseases for a number of reasons. First, modulators are directed at the immediate effects of the abnormal CFTR changing the channel function in a minority of patients who already hope for a much better quality of life and survival. Second, they give a boost of optimism to the majority of the CF population while new combination approaches are underway. Third, they change the way of thinking in CF management based on personalized medicine. Finally, they prove that effective management of the genetic defect in CF is possible and hopefully new drugs and new strategies will be able to reverse the natural cause of the disease, rendering CF an inherited disease without a life-limiting outcome.

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