The new triple combination in CFTR modulators: A new era in the management of cystic fibrosis

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Cystic fibrosis (CF) is the most common life-threatening hereditary disease in Caucasians affecting over 90000 people worldwide[1]. It is most prevalent in populations with northern European ancestry and its frequency among Caucasians varies between one in 2500–3000 live births[1]. CF is a classic Mendelian autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on the 7th chromosome. CFTR, a 1480- amino acid protein located on the apical surface of epithelial cells, functions as a channel of chloride and bicarbonate ions across epithelial surfaces and as a negative regulator of epithelial Na+ channel[1,2]. Dysfunctional CFTR leads to impaired chloride secretion and excess sodium absorption, impairs mucociliary clearance, is associated with persistent airway infection and unresolved inflammation, and leads to obstructive lung disease and progressive structural lung damage[3].

Over 2000 CFTR gene variants have been identified whereas one in 25 Caucasians are carriers of the disease. The most prevalent CF-causing mutation – the deletion of phenylalanine at position 508 (F508del) – originated in Western Europe during the early Bronze Age[2]. In Europe 40% of people with CF (PWCF) are F508del homozygotes, 41% are F508del heterozygotes and 19% have two other mutations[4]. Apart from F508del, only 6 mutations present with a prevalence of ≥1%. CFTR gene mutations are grouped into 6 classes according to whether they affect protein synthesis, protein trafficking to the apical membrane, channel gating on the cell surface, channel conductance, protein abundance or stability. Classes I-III are linked to more severe phenotypes whereas classes IV-VI are associated with milder disease[2].

CF was identified in 1938 by Dorothy Andersen, who described cystic fibrosis of the pancreas in 49 patients. The disorder was subsequently associated with lung infection and salt loss. To date, many manifestations have been identified including chronic lung infections, bronchiectasis, sinusitis, pancreatic insufficiency, gastrointestinal conditions, CF-related diabetes mellitus (CFRD), and hepatobiliary disease[1,2]. CF manifestations change with age and require specialized multidisciplinary care. Despite the variety of the affected systems over 75% of PWCF die of respiratory causes, 66% of respiratory disease and 11% of transplantation-related issues[4]. This observation underlines the fact that respiratory physicians are the leaders in every adult CF team worldwide[1].

Indeed, the majority of PWCF today are adults; according to the European CF Society patient registry in 2019, 52.4% of PWCF in Europe were adults and the percentage has been continuously increasing[4]. CF is no longer a pediatric disease and the capacity of healthcare systems to deal with the increasing number of adult patients has been identified as a potential challenge.

Management of CF remains complicated and time consuming; in fact, PWCF are required to spend 3–4 hours per day on respiratory physiotherapy and inhaled treatments[5]. In addition, current CF treatments are inadequate to provide PWCF a normal life span and CF remains a life-limiting disease. The hopes for an effective gene therapy that were raised after the discovery of the CFTR gene in 1989 were, unfortunately, not met for a number of reasons and until recently CF management was based on symptom control[6].

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More specifically management CF respiratory disease includes chest physiotherapy and exercise, eradication of *Pseudomonas aeruginosa* infections, treatment of *P. aeruginosa* infection when it becomes chronic, prompt and aggressive treatment of pulmonary exacerbations, chronic therapies to maintain lung health such as dornase-α for mucus degradation, hypertonic saline and mannitol (hydrator therapy). Furthermore, special issues such as hemoptysis and pneumothorax have to be specifically addressed and are particularly common in adults with severe disease[5]. Finally in end-stage respiratory disease, bilateral lung transplantation is the only viable solution.

During the last decade, a new approach in the management of CF has been introduced, targeting the defective CFTR protein. CFTR modulators include 3 different classes which are distinguished based on their mechanism of action. *Potentiators* such as ivacaftor increase CFTR function as a transporter on the apical membrane of the epithelial cell. On the other hand, *correctors* such as lumacaftor, tezacaftor and elexacaftor increase the transportation of the defective CFTR from the site of production to the cell surface. Finally, *amplifiers* increase CFTR production, they are mutation agnostic and are intended to be co-administered with potentiators and correctors, but none is commercially available at present[7].

It is obvious that the efficacy of each modulator class depends on the underlying genotype[8]. The four commercially available CFTR modulators are presented in Table 1. The first CFTR modulator to receive approval was ivacaftor which is administered in PWCF with at least one specific mutation such as G551D (a class III mutation) or other class IV and V mutations, which are associated with mild phenotypes and represent around 7% of PWCF[8]. The first study on the efficacy of ivacaftor, published in 2011, showed impressive results, such as increase in FEV1 of 10.6% and reduction of exacerbations of 55% compared to placebo, in 48 weeks[9]. A more longitudinal study with data from US and UK, CF patient registries assessed the 5-year effects of ivacaftor on ivacaftor-treated versus untreated PWCF matched by age, sex and disease severity based on genotype. Over the course of 5 years, ivacaftor not only improved FEV1 and reduced exacerbations and hospitalizations, but also resulted in fewer people with CFRD and *P. aeruginosa* infection. Furthermore, a statistically significantly higher probability of survival and remaining transplant-free over the course of 5 years for the US cohort and a trend toward higher probability of survival and remaining transplant-free over the course of 4 years for the UK cohort were shown for ivacaftor-treated patients suggesting disease modification by CFTR modulation with ivacaftor[10].

Unfortunately, these outstanding results are limited to a minority of rare mutations. The following two double potentiator-corrector combinations that became available and addressed a far wider spectrum of CF mutations showed much less impressive results[8]. In 2015, a randomized, double-blind, placebo-controlled, phase III study on the efficacy of the combination of lumacaftor and ivacaftor for 24 weeks in F508del homozygotes showed a 2.6–4.0% increase in FEV1 and a 30–39% reduction in exacerbations[11]. Two years later a randomized, double- blind, placebo-controlled, phase III study on the efficacy of the combination of tezacaftor and ivacaftor for 24 weeks, again in F508del homozygotes, resulted in higher FEV1 by 6.8% and lower rate of exacerbations by 35%[12]. Furthermore, the use of tezacaftor/ivacaftor was expanded to PWCL with a F508del and a residual function (mild) mutation based on the results of another double-blind, placebo-controlled study which after 8 weeks showed a 6.8% improvement in FEV1[13].

Unfortunately, although double corrector/potentiator combinations cover a significantly higher percentage of PWCF and have some stabilizing effect, they failed to show the much expected disease course modification and this was also evident in everyday clinical practice. The new true revelation in CFTR modulation came in 2019 with the triple combination which combines the effects of two correctors, the older tezacaftor and the new elexacaftor, with the potentiator ivacaftor. Middleton et al.[14] showed that administration of the triple combination for 24 weeks, in PWCF aged >12 years with a F508del and a minimal function (more severe) mutation, resulted in higher FEV1 by

Table 1. Available CFTR modulators

Drug	Age	Mutations	Clinical trials outcome		
			Duration	Decrease in exacerbations, %	Increase in FEV1, %
Ivacaftor	≥4 months	One G551D or one Class IV-V mutation	48 weeks[9]	55	10.6
Lumacaftor-Ivacaftor	≥2 years	F508del homozygous	24 weeks[11]	30–39	2.6–4
Tezacaftor-Ivacaftor	≥6 years	F508del homozygous OR F508del heterozygous and a Class IV-V mutation	24 weeks[12]	35	6.8
Elexacaftor-Tezacaftor-Ivacaftor	≥6 years	At least one F508del	24 weeks[14]	63	14.3

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14.3% and lower rate of exacerbations by 63% compared to placebo[14]. In the same year, Heijerman et al.[15], showed that administration of the triple combination, for 4 weeks in F508del homozygotes aged >12 years, resulted in a 10% additional increase in FEV1 compared to the tezacaftor-ivacaftor combination. In 2021, an open-label, phase III study on the safety and efficacy of the triple combination in PWCF aged 6–11 years also showed favorable results expanding the combination approval to patients aged >6 years[16]. Furthermore, FDA and EMA have approved the triple combination for all PWCF with at least one F508del mutation (regardless of the other one), thus covering over 80% of all PWCF.

The change that the new triple combination brought to CF management is clearly indicated by the fact that based on the US CF Foundation annual report of 2020, i.e. one year after the publication of the first two studies, out of the 23305 PWCF who were eligible to receive CFTR modulators, 63.85% were on the triple combination[17]. Although it is too soon to have longitudinal data on the effect of the new combination to the course of the disease, there are already several indications that CFTR modulation will become the next significant step in the long line of achievements in CF care. First of all, clinical experience suggests that the number of hospitalizations has dramatically decreased, nearly transforming CF to an outpatient disease. Our patients are growing healthier, heavier, with better respiratory function, less need for long-term oxygen therapy and insulin, and much more able to cope with their everyday needs. Importantly, this seems to apply to patients with very low FEV1 (<40%) who were not included in the reference studies[18]. Secondly, PWCF are starting to stop the time-consuming medications they have used nearly all their lives. In fact, a study targeting to evaluate the effect of chronic treatment discontinuation after initiation of the triple combination, is under way[19]. Thirdly, new challenges in patient care arise, for instance the use of the triple combination in patient groups for which it was either not recommended, such as transplanted patients or preferable to avoid, such as pregnant women. The use of the combination in these patient groups has already been reported, indicating favorable results[20,21]. Last but not least, in 2021, a case report described false negative newborn screening and lower than typical sweat chloride concentration in an infant who turned out to be F508del homozygous and whose mother was on CFTR modulators[22]. This case gives us a glimpse of the effects that the early, even *in utero*, administration of the triple combination may have, not only on the clinical manifestations but also on the underlying pathophysiology of the disease.

In the 1950s, life expectancy in CF was a few months, the main causes of death were meconium ileus and malnutrition[1]. Today median survival is >40 years in developed countries rendering CF an example of what development of basic science and evolution of new drugs can offer to medicine and ultimately patients. The reasons for this incredible improvement include significant milestones in CF care such as correction of nutrition deficits, airway clearance, antibiotic therapy and patients' management in specialized centers. It seems that CFTR modulators and especially the elexacaftor/tezacaftor/ivacaftor combination represent a new landmark in PWCF's lives, already affecting the way CF is perceived and CF care is provided.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

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DATA AVAILABILITY

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DISCLAIMER

The views and opinions expressed in this article are those of the authors.

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