CFTR therapy

Cftr modulators therapy

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Background

The current guidelines for the care of CF patients are based on the treatment of the secondary pathophysiological effects of CFTR malfunctioning, but over the last 25 years the role of specific drugs in the treatment of the underlying defect has been investigated.

CF disease is caused by a genetic defect of the CF Transmembrane Conductance Regulator (CFTR), that is a protein functioning as a channel to allow passage of Cl- ions and bicarbonates across the apical membrane of various epithelia.

A drug discovery program has been developed to investigate the molecular and cellular basis of CFTR mutations and to design effective treatments to enhance CFTR intracellular trafficking (correctors) and CFTR ion channel function (potentiators).

More than 2000 mutations in the CFTR gene are known to cause the channel to work improperly, they affect the quantity of the protein that reaches the cell surface or the function itself of the protein on the cell surface. CFTR mutations have been divided in six different classes: impaired biosynthesis (class I); defective protein maturation and accelerated degradation (class II); defective regulation of CFTR at the plasma membrane (class III); defective chloride conductance (class IV); diminished CFTR transcription (class V) and accelerated turnover at the cell surface (class VI).

The major advantage of the classification is the possibility of adopting the same therapeutic strategy for each class, even if, in the future, this stratified approach tailored to a specific functional class of mutations in CFTR, can be refined further to an individual level by exploiting recent advances in ex vivo drug testing methods (Ikpa PT, 2014), (Martiniano SL, 2016), (JM Beekman JM, 2016).

Corrective treatments that are non-specific to mutation class and thus applicable to all patients, as gene therapy, cell-based therapies, and activation of alternative ion channels that bypass CFTR are being explored, but they are still in early stages of development. (De Boeck K, 2016)

In the international literature, it has been summarized the good results achieved by CFTR modulators in terms of clinical impact (Bell SC, 2015) (Amaral MD, 2015), but, also the problems associated with the new therapy (Mayer-Hamblett N-2016) and, in particular:

- the necessity to have new biomarkers to valuate efficacy and tolerability (K De Boeck, 2014);
- the difficulty to project placebo-controlled trials (VanDevanter DR, 2017);
- the possibility that chronic treatment with CFTR potentiators and correctors may have unexpected effects that cannot be predicted from short-term studies (Cholon DM, 2014);
- the clinical and ethical dilemmas about the high price of these drugs (Jones AM, 2015);
- the possible impact on fertility (Jones GH, 2015) and on pregnancy (Goss CH, 2016), (Heltshe SL, 2017).

The potentializer VX-770 (Ivacaftor) has been the first CFTR modulator able to demonstrate to be effective in CF.

It is an oral medication given twice daily and has shown benefits, in CF patients who carry the class III mutations, on lung function, sweat chloride normalization, weight gain, patient-reported quality of life and respiratory exacerbations (R O'Reilly, 2013).

Up to now, the FDA (USA), the Health Canada, the European Medicines Agency (EMA) and, specifically in Italy, the Italian Agency for drugs (AIFA), have approved Ivacaftor (Kalydeco® by Vertex Pharmaceuticals) for the treatment of CF in patients aged ≥ 6 years who have class III gating mutations (G551D, 178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P, or G1349D) and for patients who have the R117H mutation.

In USA the drug is approved from the age of 2 years on.

FDA and EMA have approved Ivacaftor in combination with the corrector VX-809 Lumacaftor (ORKAMBI™ by Vertex Pharmaceuticals) to treat people with Cystic Fibrosis ages 6 and older, who have two copies of the F508del mutation. About ORKAMBI recently some concerns have been emerged, in observational studies, about relatively high rate of drug intolerance, above all in patients with more advanced lung disease (Jennings MT, 2017).

In the 2017 Cystic Fibrosis Foundation drug development pipeline, 19 compounds, besides Kalydeco and Orkambi, are taken into consideration regarding to restore CFTR function: 1 in phase three, 8 in phase two, 2 in phase one and 6 in pre-clinical phase.

Issues

Safety and efficacy of corrective treatments applicable to all patients as non-specific to mutation class

Identification of CFTR correctors or potentiators and related mutation targets

Features of CF candidates for therapy with CFTR modulators

Impact of CFTR modulators on clinical outcomes (respiratory condition, quality of life, survival, nutritional parameters, sputum,
Sensitivity and specific surrogate biomarkers to investigate the efficacy of CFTR modulators

Safety of CFTR modulators, also for long time treatments.

What is known

One RCT, published in 2002, investigated the safety and efficacy of a single dose of dipropylxanthina (CPX) in 30 F508del homozygous patients; no effects were demonstrated on transepithelial nasal potential difference (NPD) and sweat test values.

One RCT, published in 2002, studied the safety and efficacy of three doses of 4phenylbutyrate in 19 F508del homozygous patients; the minimum tested dose (20 mg) showed good tolerability and a significant induction of chloride transport.

One RCT, published in 2003, studied the safety and efficacy of gentamicin three times a day for 14 days in 19 CF patients hetero- or homozygous for stop-mutations and F508del; a significant induction of chloride transport was demonstrated on NPD only in patients with at least one stop-mutation.

Gentamicin plus tobramycin was also studied in another RCT, published in 2007, in 11 and 18 CF patients with and without stop-mutation, respectively: no effects were demonstrated on NPD value.

One RCT, published in 2010, studied the safety and efficacy of Ataluren (PTC124) in 30 CF patients with a nonsense mutation (class I mutations) in at least one allele: a significant induction of chloride transport was demonstrated on NPD and the drug was well tolerated.

In May 2014 a study about Ataluren for the treatment of patients with nonsense-mutation has been published: Ataluren did not improve lung function in the studied patients, but it has been speculated that the drug might be beneficial for patients not taking chronic inhaled tobramycin.

In 2016, a Cochrane Database Protocol has stated the necessity to evaluate benefits and harms of Ataluren and similar compounds on clinically important outcomes in people with CF with class I mutations.

In November 2016 a Cochrane Review, about this topic, has included two parallel randomised controlled trials in which Ataluren was compared to placebo for a duration of 48 weeks in 238 participants (age range 6 to 53 years). It has been concluded that there is, currently, insufficient evidence to determine the effect of Ataluren as a therapy for CF people with class I mutations.

In 2012 a RCT about the impact of miglustat did not show any significant changes in the total chloride secretion assessed by nasal potential difference, in sweat chloride or in lung function values.

Ivacaftor clinical efficacy in patients with G551D mutation was stated, in 2014, by a Health Tecnology Assessment, even if the high cost and the lack of data about long-term effectiveness have been stressed.

In February 2014 Ivacaftor has been shown (KONNECTION study) to be safe and to improve lung function, BMI, sweat chloride and CFQ-R in CF patients 76-years-old with CFTR gating mutations class III, other than G551-D.

In March 2014 Ivacaftor has demonstrated clinical benefits in CF patients with FEV1 lower than 40% and/or lung transplant listing.

One Cochrane Database Review published in March 2015 about the role of CFTR Modulators as specific therapies for class II, III and IV mutations, included four RCT (378 patients, followed from 28 days to 48 weeks). Three RCT enrolled patients with the G551D mutation: one phase 2 trial (19 patients enrolled) and two phase 3 trials (167 adult patients and 52 pediatric patients enrolled). The fourth trial enrolled 140 patients homozygous for the F508del mutation. Both G551D phase III trials demonstrated a clinically relevant impact of the potentiator VX-770 (Ivacaftor) on the studied outcomes at 24 and 48 weeks and provided evidence for the use of this treatment in adults and children (over six years of age) with this class III mutation. In August 2015 a RCT showed that nutritional status improved following treatment with ivacaftor for 48 weeks.

In July 2015, Ivacaftor has shown (KONDUCT study) a significant improvement in sweat chloride values and CFQ-R respiratory domain scores in adult patients with R117H mutation who have established disease.

In 2015 a post-hoc analysis suggested that the majority of patients with G551D-CFTR and clinical characteristics similar to those present in patients enrolled in the previous phase 3 RCT have the potential to benefit from ivacaftor therapy.

In 2016 a study evaluated how ivacaftor treatment had affected CF symptoms, functioning, and well-being, measured by the Cystic Fibrosis Questionnaire-Revised (CFQ-R) and showed broad benefits across domains respiratory symptoms, physical and social functioning, health perceptions and vitality.

In 2014, in a phase II RCT, VX-809 (Lumacaftor), a corrector of CFTR, combined with Ivacaftor, was studied in subjects Homozygous for F508del. The results supported a further exploration of the combination therapy as a treatment in this setting.

In 2015, two (TRAFIC and TRANSPORT) phase 3 RCT have shown that Lumacaftor in combination with Ivacaftor, in patients 12 years of age or older, have provided a benefit for enrolled patients in terms of lung function and rate of pulmonary exacerbations.

In 2016, a pooled analysis of the two trials, in which efficacy and safety data have been considered in subgroups based on baseline ppFEV1, confirmed that lumacaftor/ivacaftor combination therapy benefits patients with cystic fibrosis homozygous for Phe508del CFTR who have varying degrees of lung function impairment.

In the same year another study demonstrated that the long-term safety profile of lumacaftor/ivacaftor was consistent with previous RCTs. Benefits continued to be observed with longer-term treatment: lumacaftor/ivacaftor was associated with a 42% slower rate of ppFEV1 decline than in matched registry controls.

In 2017 lumacaftor/ivacaftor therapy has been proved to improve sweat chloride and respiratory symptom scores in patients Heterozygous.
Unresolved questions

Sensitive and specific surrogate biomarkers to investigate the efficacy of CFTR modulators.

CFTR modulators efficacy and safety evaluated at longer follow up.

Efficacy and safety of new therapeutic protocols focused on other mutations than class III and F508del mutations.

Several studies are ongoing:

A Phase 3, randomized, double-blind, ivacaftor-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of VX-661 in Combination With Ivacaftor in subjects aged 12 years and older with CF who are heterozygous for the F508del-CFTR mutation and a second CFTR allele with a gating defect that is clinically demonstrated to be ivacaftor responsive. NCT02412111

A Phase 2, Randomized, Double-Blind, Placebo Controlled, Parallel-Group, Exploratory Study to Evaluate Effects of VX-661 in Combination With Ivacaftor on Lung and Extrapulmonary Systems in Subjects Aged 18 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation. NCT02508207

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the F508del-CFTR Mutation and With a Second CFTR Mutation That Is Not Likely to Respond to VX-661 and/or Ivacaftor Therapy (F508del/NR) NCT02516410

A Phase 3, Double Blind, Placebo Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years, Homozygous for the F508del CFTR Mutation. NCT02514473

A Phase 3 study about Efficacy and Safety of Ataluren in patients with nonsense mutations not receiving chronic inhaled aminoglycosides. NCT02139306

A Phase 2 study to assess the Safety, Tolerability, Pharmacokinetics and preliminary pharmacodynamics of QBW251 in healthy subjects and cystic fibrosis patients following single and multiple doses. NCT02190604

A Phase 2 study to evaluate the safety and efficacy of treatment with ENaC Inhibitor VX-371 in saline compared to saline alone in subjects with cystic fibrosis (CF) who are 712 years of age, homozygous for the F508del CFTR mutation, and being treated with Orkambi. NCT02709109.

A Phase 2 study to evaluate the treatment effect of VX-661 in combination with ivacaftor on chest imaging endpoints using low-dose computed tomography (LDCT) at Week 72, and to evaluate the safety of VX-661/ivacaftor through Week 72 NCT02730208

A Phase 3b, 2-part, Randomized, Double-blind, Placebo-controlled Crossover Study With a Long-term Open-label Period to evaluate the efficacy, measured by lung clearance index (LCI), of ivacaftor treatment in subjects With Cystic Fibrosis Aged 3 Through 5 Years, Who Have a Specified CFTR Gating Mutation. NCT02742519

A Phase 2 study Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to investigate the efficacy and safety of N91115 in adult patients with CF who are homozygous for the F508del CFTR mutation and being treated with lumacaftor/ivacaftor. NCT02589236

A Phase 4 Study of the Effects of Lumacaftor/Ivacaftor on Exercise Tolerance in Subjects With Cystic Fibrosis, Homozygous for the F508del CFTR Mutation NCT02875366. A Phase 4 study to evaluate the use of smart adherence technology to measure medication adherence in CF patients Homozygous for the F508del CFTR Mutation NCT02823470

A Phase 2, randomized, double-blind controlled , multicenter study to evaluate the safety, tolerability, and efficacy of VX-440 in dual and triple combination with tezacaftor (TEZ; VX-661) and ivacaftor (IVA; VX-770) in CF patients homozygous for the F508del CFTR mutation, or who are heterozygous for the F508del mutation and a minimal function (MF) CFTR mutation not likely to respond to TEZ and/or IVA therapy (F508del/MF). NCT02951182

A Phase 2, randomized, double blind controlled , multicenter study designed to evaluate the safety and tolerability of VX-152 in Triple Combination (TC) with tezacaftor (TEZ; VX-661) and ivacaftor (IVA; VX-770) in CF patients heterozygous for the F508del CFTR mutation and a minimal function (MF) CFTR mutation not likely to respond to TEZ and/or IVA therapy (F508del/MF), or who are homozygous for the F508del CFTR mutation. NCT02951195

A Phase 2, Randomized, double-blind controlled study to evaluate the safety and efficacy of different dosages of CTP-656 with placebo and an open-label active comparator (VX-770) in CF patients with CFTR gating mutations. NCT02971839

A Phase 3 randomized, controlled, crossover study to evaluate the efficacy of Ivacaftor in CF patients who are 6 years of age and older and have either a 3849 + 10KB C?-T or D1152H CFTR mutations. NCT03068312

A Phase 2a, randomized, controlled study to evaluate GLPG2222 in Ivacaftor-treated adult CF patients harbouring one F508del CFTR Mutation and a second gating (Class III) mutation. NCT03045523.

Keywords
G551D-CFTR; Cystic Fibrosis Transmembrane Conductance Regulator;