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 recently, a new type of CFTR modulators is under investigation: amplifiers, that increase the amount of CFTR protein in the cell, making more CFTR available for other CFTR modulators to work on.

More than 2000 mutations in the CFTR gene are known to cause the channel to work improperly, because 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. In the future, however, this approach tailored to a specific functional class of mutations in CFTR, could be refined further to an individual level by exploiting recent advances in ex vivo drug testing methods (Ippa PT, 2014), (Martiniano SL, 2016), (JM Beekman JM, 2016). The possibility to inhibit the epithelial sodium channel (ENaC) and potentially activate alternative chloride channels, has been studied and CRISPR-Cas9, one of the most promising tool for gene editing that provides researchers the opportunity to modify gene function, has been speculated to be possibly applicable also in CF disease (Marangi M, 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 associated problems (Mayer-Hamblett N, 2016) and, in particular, the necessity to have new biomarkers to valuate efficacy and tolerability (K De Boeck, 2016); the difficulty to project placebo-controlled trials (VanDevanter DR, 2017); the possibility that chronic treatment with CFTR modulators might have unexpected effects that cannot be predicted from short-term studies (Chotlon 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), (Heitelshe SL, 2017).

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

It is an oral medication and it 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).

In USA the drug is approved for patients from the age of 2 years with gating mutations, for patients with R117H mutation and for patients with some residual function mutations (2789+5G—>A, 3272—>26A—>G, 3849+10kbC—>T, 711+3A—>G e E831X).

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, 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 2018 Ivacaftor in combination with the other corrector VX -661 Tezacaftor (SYMDEKO™ by Vertex Pharmaceuticals) has been approved in USA and in Canada to treat patients aged 12 years and older who have two copies of the F508del mutation, or who have at least one mutation that is responsive to treatment with SYMDEKO (711+3A?G, A455E, D579G, E193K, K1060T, R117C, S945L, 2789+5G?A, A1067T, D1152H, E831X, L206W, R347H, S977F, 3272-26A?G, D110E, D1270N, F1052V, P67L, R352Q, 3849+10kbC?T, D110H, E56K, F1074L, R74W, R1070W) Recently (Ren CL, 2018) the Cystic Fibrosis Foundation has published recommendations about CFTR modulators in CF patients.
Issues

Safety and efficacy of corrective treatments applicable to all patients as non-specific to mutation class
Identification of CFTR correctors or potentiatiors 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, radiological findings)
Sensitive and specific surrogate biomarkers to investigate the efficacy of CFTR modulators
Safety of CFTR modulators, also for long time treatments.

What is known

A Cochrane Review (Southern SW, 2018) concluded that there is insufficient evidence that monotherapy with CFTR modulators in CF patients with 2 copies of F508del mutation has clinically important effects. Otherwise combination therapies (Lumacaftor-Ivacaftor and Tezacaftor-Ivacaftor) have similar small improvements in clinical outcomes: quality of life has moderate-quality evidence; respiratory function has high-quality evidence; lower pulmonary exacerbation rates have moderate-quality evidence. Lumacaftor-Ivacaftor is associated with an increase in early transient shortness of breath and longer-term increases in blood pressure; these effects were not observed for Tezacaftor-Ivacaftor, but safety data for children under 12 years of age are not available.

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 4-phenylbutyrate 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: Atalauren 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 of 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 improvements 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 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 with cystic fibrosis homozygous for F508del-CFTR.

In 2017 an RCT explored the effect of Tezacaftror/ivacaftor combination in F508del homozygous patients aged 12 years and above: the effects on the absolute and relative changes in the percentage of the predicted FEV1 in favor of tezacaftror–ivacaftor over placebo were 4.0 percentage points and 6.8%, respectively.

Another RCT published in 2017 regarding treatment with Lumacaftor and Ivacaftor revealed that this combination was associated with statistically significant improvements in lung function, as measured by LC12.5 and ppFEV1, versus placebo in patients aged 6–11 years with cystic fibrosis homozygous for F508del-CFTR.

In 2016 several studies have evaluated the safety and efficacy of lumacaftor/ivacaftor therapy in patients homozygous for F508del mutation who have varying degrees of lung function impairment. The combination therapy was associated with a 42% slower rate of ppFEV1 decline than in matched registry controls.

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Unresolved questions

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

CFTR modulators efficacy and safety evaluated at longer follow up.

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: completed, results not available)

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 (NCT02588207: completed, results not available)

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: completed, results not available)

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: results available)

A Phase 3 study about Efficacy and Safety of Ataluren in patients with nonsense mutations not receiving chronic inhaled
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: study terminated, results available)

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 >12 years of age, homozygous for the F508del CFTR mutation, and being treated with Orkambi. (NCT02709109: completed, results not available)

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: not recruiting patients)

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: study terminated, results not available)

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: completed, results not available)

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: completed, results not available))

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: study terminated, results not available)

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: completed, results not available)

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 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: recruiting)

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: study terminated, results not available)

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 mutation (NCT03068312: recruiting)

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: completed, results not available)

Phase 2, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy of LUM/IVA, in subjects with CF 12 years of age and older who have at least one A455E mutation (NCT03061331: completed, results not available)

A Phase 3, 2-arm, multicenter study with an open-label Ivacaftor arm and an observational arm to evaluate the safety and efficacy of long-term ivacaftor treatment in subjects with cystic fibrosis (CF) who are <24 months of age at treatment initiation and have a CFTR gating mutation (NCT03277196: recruiting)

A first-in-human and proof-of-concept study of VX-445. The study includes 6 parts. Parts A, B, and C will be conducted in healthy subjects. Parts D, E, and F will be conducted in subjects with Cystic Fibrosis (CF) who are homozygous for the F508del mutation of the CF transmembrane conductance regulator (CFTR) gene (F/F genotype), or who are heterozygous for the F508del mutation and a minimal function (MF) CFTR mutation not likely to respond to TEZ, IVA, or TEZ/IVA (F/MF genotypes) (NCT03227471: recruiting)

A Phase 2, randomized, double-blind, placebo- and tezacaftor/ivacaftor (TEZ/IVA)-controlled, parallel-group, 3-part, multicenter study designed to evaluate the safety and efficacy of VX-659 in triple combination (TC) with TEZ and IVA in subjects with cystic fibrosis (CF) who are homozygous for the F508del mutation of the CF transmembrane conductance regulator (CFTR) gene (F/F genotype), or who are heterozygous for the F508del mutation and a minimal function (MF) CFTR mutation not likely to respond to TEZ, IVA, or TEZ/IVA (F/MF genotypes) (NCT03224351: recruiting)

Study VX16-661-114 (Study 114) is a Phase 3b, randomized, double-blind, placebo-controlled, parallel group, multicenter study in subjects aged 12 years and older with CF who are homozygous for the F508del mutation on the CFTR gene and who discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment. This study is designed to evaluate the safety and efficacy of VX/IVA (NCT03160719: recruiting)

This study will evaluate the efficacy of ivacaftor treatment in subjects with CF 6 years of age and older who have a 3849 + 10KB C>T or D1152H CFTR mutation (NCT03068312: recruiting)

A Phase I/II trial (NCT03375047: will evaluate safety and tolerability in adults of MRT5005 administered by nebulization in single and multiple escalating doses. The delivery of the drug to bronchial epithelial cells following multiple doses will be assessed
and its biological activity by measuring changes in CFTR protein levels and CFTR chloride channel activity post-treatment. will be characterized.

An ongoing trial (NCT03278314) will evaluate Tezacaftor/Ivacaftor therapy expanded access program for patients 12 years and older.

A phase 3 ongoing trial (NCT03447249) of VX-659 Combination Therapy in Subjects With Cystic Fibrosis Heterozygous for the F508del Mutation and a Minimal Function Mutation.

A phase 3 ongoing trial (NCT03460990) of VX-659 in triple combination with tezacaftor and ivacaftor in Subjects Homozygous for F508del.

A phase 2 ongoing trial (NCT03474042) to evaluate GLPG2737 administered orally to homozygous for the F508del CFTR mutation and on stable treatment with Orkambi.

A phase 3 ongoing trial (NCT03559062) will evaluate the efficacy of tezacaftor in combination with ivacaftor (TEZ/IVA) in subjects aged 6 through 11 years, who are homozygous for the F508del or heterozygous for F508del with an eligible residual function mutation.

In the Drug Development Pipeline 2018, besides Kalydeco, Orkambi and Symdeko, already available for the patients, 16 compounds are taken into consideration regarding to restore CFTR function: two in phase 3 *VX 445 + tezacaftor + Ivacaftor; *VX559+Tezacaftor +Ivacaftor five in phase 2 *QBW251, *FDL169 (a new CFTR corrector ) *GLPG2222, *PTI-428 (a CFTR amplifier). *VX-561(an altered form of potentiator Kalideko); four in phase one: *PTI-801 (a new CFTR corrector) *PTI-808 (a new CFTR potentiator),* QR-010 (an oligonucleotide designed to repair CFTR-encoded mRNA), MRT5005; five in pre-clinical phase handled by *Editas (a program to explore ways to correct common and rare mutations in the CFTR gene using CRISPR/Cas approaches) *Genzyme/Sanofi a program to identify new therapies in people who have the F508del mutation. *Pfizer (a program to identify new therapies in people who have the F508del mutation. *Reata (a program to expand the number of therapies in people who have the F508del mutation. *Southern Research Institutes (a program to identify potential therapies for nonsense mutations)

A phase 2 trial to evaluate efficacy and safety of Lenabasum in CF patients is ongoing (EUCTR2017-003723-29)

**Keywords**

G551D-CFTR; Cystic Fibrosis Transmembrane Conductance Regulator; Ivacaftor; Lumacaftor; Tezacaftor; VX-661; VX-770; VX-809;