Ivacaftor in French patients with cystic fibrosis and a G551D mutation in the real world setting

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Objectives: Ivacaftor, a CFTR potentiator, is indicated in patients with CF 6 years and older carrying a G551D mutation. It has been available in France since April 2012. Our aim was to review the first data with Ivacaftor therapy in French patients in clinical practice.

Methods: An independent retrospective survey was sent by e-mail to physicians from French CF centres to identify patients treated with Ivacafor. Collected information included birth date, gender, date of first treatment with Ivacaftor, FEV1 and weight at treatment initiation, after one, 3 and 6 months of treatment, adverse events and any treatment interruption.

Results: Survey included 48 patients from 23 CF centres (27 males, 21 females), with a mean age of 21.3 yo (6.1 to 51.8) over the April to November 2012 period. Fourteen patients were children aged 6–12 yo. Baseline mean FEV1 (±SD) was 71.3 (±25.9)% pred. There was an increase from baseline of 8.5 (±7.7), 9.4 (±8.0) and 11.0 (±8.0) percentage points of predicted FEV1, respectively at Months 1 (n=41), 3 (n=35) and 6 (n=20). Weight increased from baseline of 1.0 (±1.4), 2.3 (±1.1) and 3.2 (±2.7) kg, respectively at Months 1, 3 and 6. Adverse events considered severe drug related included headache (n=4), nausea (n=2), abdominal pain (n=1), asthenia (n=1), dizziness (n=1), skin rash (n=1), and breast hypertrophy (n=1). Two patients interrupted Ivacaftor from D7 to D35, one for rash, one for digestive symptoms; events did not re-occur when Ivacaftor treatment was resumed.

Conclusions: Preliminary results with Ivacaftor in French CF patients in real world setting were similar to clinical study data, in efficacy (increase in FEV1 and weight) and safety.

Pulmonary exacerbations in CF patients with the G551D-CFTR mutation treated with ivacaftor

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In Phase 3, 48-week studies of CF patients (pts) with the G551D mutation, ivacaftor provided benefits, including improved lung function, sweat chloride and fewer pulmonary exacerbations (PEs). We analyzed data from Studies 102/103 to better understand the clinical diagnosis and treatment of PEs. In Studies 102 (⩾12 yrs, N=161) and 103 (6–11 yrs, N=52) a change in antibiotic therapy for any of 12 protocol-defined signs or symptoms was called a sinopulmonary event (SPE). SPEs with ≥4 signs or symptoms were defined as a PE. Over 48 weeks, there were 146 PEs in 72 pts (⩾12 yrs) and 12 PEs in 11 pts (6–11 yrs). PEs and SPEs are summarized in the Tables.

Pts treated with Ivacaftor had fewer PEs and SPEs than controls. Although young pts (6–11 yrs) experienced fewer PEs overall, the percentage of young pts having SPEs was comparable to the older pts. Pts treated with Ivacaftor had fewer PEs and SPEs than controls. Although young pts (6–11 yrs) experienced fewer PEs overall, the percentage of young pts having SPEs was comparable to the older pts. There was no significant benefit in patients with DF508. Ivacaftor was well tolerated.

Conclusions: Ivacaftor has a profound impact on clinical outcomes at 48 weeks in patients with G551D. There is no evidence to support its use in patients with DF508. RCTs in children less than six years of age are needed.

A Cochrane review of CFTR potentiators in cystic fibrosis

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Objectives: By improving CFTR function, potentiators (eg Ivacaftor) may correct abnormal epithelial salt transport in certain mutation classes. We systematically reviewed randomized controlled trials (RCTs) of potentiators in CF.

Methods: We included parallel design RCTs, published or not, evaluating potentiators in children or adults with CF. Primary outcomes were FEV1, survival, and quality of life (QoL). Secondary outcomes included weight and sweat chloride. Published RCTs were assessed for risk of bias using Cochrane methodology. Where appropriate, trial results were synthesized.

We included six placebo-controlled trials. Three RCTs evaluated Ivacaftor in 231 patients with G551D; two evaluated Ivacaftor added to a corrector (VX809) in 171 patients with DF508; one evaluated Ivacaftor without corrector in 140 patients with DF508. No trial included children less than six years of age. Of the three RCTs that have been published, two were rated as high risk of outcome reporting bias. All three were rated as low or unclear risk of other types of bias. Synthesis of results of two RCTs, in patients with G551D, was possible (pooled data showing mean change from baseline [95%CI]): QoL measured with CFQR (7.85 [4.90, 10.83]), % predicted FEV1 (10.4 [8.6, 12.83]); sweat chloride (−49.8 mmol/l [−54.7, −44.9]); weight (2.75 kg (1.75, 3.74)). There was no significant benefit in patients with DF508. Ivacaftor was well tolerated.

Conclusions: Ivacaftor has a profound impact on clinical outcomes at 48 weeks in patients with G551D. There is no evidence to support its use in patients with DF508. RCTs in children less than six years of age are needed.

Permanent correction of >80% of disease-causing mutations in human CF cells

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We recently published the first description of correction of a CF causing mutation (AF508) in a tracheal epithelial cell line by homology directed repair (HDR) using zinc finger nucleases (ZFNs) and a donor plasmid (Lee et al., 2012). At present the approach is limited to correcting one mutation. To address this, we are using our existing cfr-specific ZFNs to target the more frequent mutation, intron 9 with the aim to correct CF mutations throughout exons 10–24 (>80% of all CF mutations) with a single ZFN pair/donor plasmid. As proof-of-principle that our ZFNs can target exogenous sequences to intron 9 we first sought to precisely incorporate a 7 bp Tag sequence into the cfr gene at the ZFN target site by HDR using a 1.5 kb donor plasmid. Analysis of cells treated with our ZFNs and donor by nested PCR revealed that the Tag can be successfully introduced into the cfr gene at the correct location.

To effect gene repair, the mini-gene repair construct requires a promoterless cfr partial DNA (exons 10–24) with appropriate splice acceptor and poly A sites. Incorporation of the mini-gene would result in full length corrected CFTR mRNA production that is under the control of the endogenous promoter, a major limitation experienced when delivering exogenous cDNA. Li et al., 2011, previously replaced exons 2–8 of the F9 gene restoring haemostasis in haemophilic mice using this strategy. Successful gene correction using a mini-gene would result in normal spatiotemporal expression of the corrected CFTR gene, that is permanent for the lifetime of the cell and is not subject to gene silencing. It could be of use as an alternative strategy to DNA addtion for gene therapy.