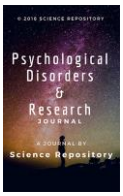

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Research Article

Cognitive Function in Cystic Fibrosis and CFTR Modulator Therapy

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ABSTRACT

Background: Cystic fibrosis is not typically associated with cognitive dysfunction that is easily discernible. Whether having a *CFTR* mutation has a direct effect on the CNS function is yet to be elucidated, despite widespread expression of the CFTR protein throughout the human nervous system.

Methods: We aimed to study the effects of *CFTR* modulators ivacaftor and lumacaftor/ivacaftor on cognition in two separate CF cohorts. These were ivacaftor, in CF patients with at least one copy of the G551D mutation, and lumacaftor/ivacaftor in homozygous F508del subjects. Using a panel of cognitive testing tools (MOCA, TMT, Cogstate™) targeting various domains that included executive function, memory and attention.

Results: The two cohorts improved significantly on *CFTR* modulator treatment when measured by the MOCA, TMT and by a combined cognitive score. Most prominently, these represent improvements in executive function.

Conclusion: Suggested CNS effect of *CFTR* mutation in CF and the impact of CFTR modulators on this.

Introduction

Cystic fibrosis (CF) is an autosomal recessive condition, resulting from mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene located on the long arm of chromosome 7. *CFTR* functions as an apical anion channel, transporting chloride and bicarbonate across the cell membrane [1]. Recent evidence suggests that *CFTR* may be an autosomal regulator of mitochondrial function [2]. There are six currently recognised classes of *CFTR*-gene mutations; classified according to the mechanism by which the CFTR protein is affected. Disease severity and prognosis are related to the class of mutation and subsequent function of *CFTR* in any affected individual [3]. Although *CFTR* is typically found on epithelial cells in the respiratory tract, gastrointestinal tract, pancreas, vas deferens and sweat glands, there is evidence that *CFTR* is present in the brain and spinal cord [4, 5]. Initially *CFTR* distribution in the brain was thought to be restricted to the hippocampus, but there is now known to be a widespread expression in neuronal cells throughout brain tissue [5, 6]. The fundamental implications of *CFTR* mutation on CNS function are currently unknown. *CFTR* has been found to be widely distributed from an early stage during neuronal development and a delay in the maturation of brain structures in individuals with CF has been identified. Furthermore, *CFTR* expression in the hypothalamus appears to be down-regulated in individuals with Alzheimer's Disease, when compared with controls [7, 8].

CFTR modulator therapy, developed over the last decade, targets specific *CFTR* channel defects and currently includes potentiator and corrector therapies. Potentiator agents increase the likelihood of existing *CFTR* channels to be functional; the first widely available agent being ivacaftor (IVA). Correctors, such as lumacaftor (LUM), improve the expression of *CFTR* at the cell surface. IVA monotherapy is the treatment of choice for individuals with CF who have class 3 gated mutations, the G551D mutation being the most common. Ivacaftor in combination with lumacaftor (LUM/IVA) is effective in individuals with

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CF who are homozygous for the F508del-*CFTR* mutation. A 10% improvement in lung function has been found in individuals who have a gating mutation and received ivacaftor monotherapy [9]. This improvement is less marked in those with the more severe F508del/F508del mutation treated with LUM/IVA [10]. However, both treatments improve lung function, reduce the rate of lung function decline and reduce exacerbation frequencies [9, 10]. The addition of newer next-generation molecules has been shown to achieve a 14% increase in percent predicted FEV1 with phase 2 clinical trials [11].

There has also been a reported improvement in the quality of life associated with modulator therapy [12]. These may be in part mediated by CNS effects. Individuals with CF are known to often experience psychosocial difficulties, with the prevalence of depression and anxiety in individuals with CF up to 2-3 times greater than the community controls [13, 14]. Moreover, in preliminary studies, individuals with CF have been found to have cognitive deficits, with greater changes identified in those with CF-related diabetes [15]. As there is evidence of *CFTR* expression in human neuronal cells, CFTR modulator therapy may provide an additional benefit in terms of improvements in cognition where *CFTR* function is potentially important. We have recently reported CNS abnormalities in CF patients [16]. Furthermore, we have found that IVA and its metabolites have off-target effects on brain tissue [17]. These include binding to receptors for neurotransmitters such as 5-hydroxytryptamine (5-HT), resulting in potential clinically relevant effects on mood, anxiety and cognition [17]. Here we report data collected in two separate studies where eligible individuals with CF were treated with either IVA monotherapy or LUM/IVA combination therapy according to their *CFTR*-mutations. An assessment of cognitive function, in addition to other parameters, was undertaken using well-characterized inventories.

Methods

I Ivacaftor Study in G551D Subjects

This was undertaken as a single-center, double-blind, placebo-controlled, randomized, crossover study. Individuals with CF, who had a least one copy of the G551D mutation were invited to participate, as described previously [12]. Briefly, this group received IVA 150mg, oral, twice daily for four weeks, or placebo, followed by a four-week washout period, then the alternative, followed by an open-label extension. Project approval was obtained from the institutional ethics committee at The Alfred Hospital (IEC339/13).

Twenty eligible participants underwent screening tests (day -28), which were repeated at randomization (day 0). These included sweat chloride measurements, routine biochemistry, lung function, bioimpedence analysis and cognitive testing in the form of Montreal Cognitive Assessment (MOCA) and Trail Making Test (TMT) A [18, 19]. Patients were assigned (1:1) to active or placebo treatment. All tests were repeated after Treatment Period 1 (day 28), the 28-day washout period (day 56) and the crossover period Treatment Period 2 (day 84). Further testing occurred on day 224 following open-label IVA treatment for 140 days (+/- 7 days). While the primary outcome was exercise tolerance, secondary endpoints were: the change in cognitive function as measured by MOCA and TMT A between placebo and active groups after the 28-day treatment period and pre- and post-open label extension (all subjects on IVA) of cognitive function as measured by MOCA and TMT A. Results related to exercise and well-being have previously been reported [12]. Training effect was controlled using a placebo and crossover design.

II Combination/LUM/IVA Initiation Study in Homozygous F508del Subjects

The LUM/IVA Study was conducted at the same site and was a single-center longitudinal evaluation of individuals with CF who were homozygous for the F508del mutation. Project approval was obtained from the institutional ethics committee at The Alfred Hospital (722/18). Individuals were recruited via the LUM/IVA combination therapy special access scheme (SAS). Individuals were eligible for the SAS if they had an FEV1 <40% predicted at the time of assessment and had no known history of mental illness (n=21). Subsequently, further patients (n=11) were included with FEV1>40% as the scheme was expanded to include all F508del homozygous patients. At baseline, 6- and 12-months participants were assessed in terms of lung function, weight, BMI, MOCA, TMT A and B and a Cogstate™ battery testing attention, processing, speed, working memory and executive function. Twenty-one participants completed treatment and were assessed over the 12-month treatment period. The primary outcome of this study was the evaluation of a cognitive function at baseline and after 12 months of LUM/IVA therapy.

MOCA is a thirty-point rapid screening test for mild cognitive dysfunction that assesses multiple cognitive domains, including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations and orientation. Scores above 26/30 are considered normal [20]. TMT is a neuropsychological test assessing visual attention and task switching. Individuals have to join 25 numbers in circles together (Part A) and then join numbers and letters together, also testing executive function (Part B) [19, 21].

Cogstate™ is an online, computer-based neuropsychological test that evaluates several cognitive domains, including verbal learning and memory, processing speed, working memory, executive speed and identification speed [22]. As part of the Cogstate™ evaluation, the following four tests were performed. i) Identification test is a card game where the subject must answer “is the card red?” this test requires attention as the primary cognitive domain and measures speed of performance/reaction time and accuracy [22, 23]; ii). The Groton Maze test uses an executive function to “find the hidden pathway” in the same maze repeated five times and measures the duration and the number of errors made completing the task; iii) The International shopping list (ISL) practices the subject’s verbal learning to remember twelve items read out by the investigator in three consecutive trials, observing duration and number of correct responses. iv) One Back is a second card game that involves identifying whether a card displayed is the same as the one prior, using working memory to do so. Test scores were calculated and measured against baseline values and, where possible, aged-matched normalised values. A compound cognitive score (CCS) for all tests was calculated by combining the mean percentage improvement of each individual test (Table 1).

GraphPad Prism (version 7) was used for calculations of mean and standard deviation, and Student's paired *t* tests were used for comparisons between time points for normally distributed variables. Percentage improvement (Table 1) was sign-corrected for the direction of change.

Table 1: Percentage improvement from baseline on LUM/IVA therapy at 6 and 12 months (* $p < 0.05$; ** $p < 0.01$).

	6 months		**12 months**	
		n		n
MOCA	3.54%	20	5.72%**	21
TMT A	15.65%*	18	12.43%	19
TMT B	4.22%	18	22.15%**	19
ISL correct	3.75%	21	-0.22%	17
ISL speed	28.49%	21	17.23%**	17
Identification score	-1.35%	22	3.66%*	17
ID speed	-3.93%	22	-11.22%**	17
ID accuracy	-1.29%	22	1.67%	17
One Back score	4.02%**	23	1.47%	17
OB speed	11.90%**	23	4.57%	17
OB accuracy score	-0.81%	23	6.09%	17
OB accuracy	-2.57%	23	6.51%	17
Maze score	1.29%	23	3.81%*	17
Maze errors	6.69%	23	20.21%*	17
Compound cognitive score (CCS)	5.09%*		6.20%*	

Results

Subject demographics for both studies are displayed (Table 2). Subsequent Cogstate™ results for the LUM/IVA study do not include the complete cohort, as some subjects did not attend all follow-up assessments within the study timeframe.

Table 2: Baseline demographics for IVA and LUM/IVA CFTR modulator studies.

	Ivacaftor Baseline Demographics n=20	**Combination Baseline Demographics n=32**
Age – mean years	32.5 (18-65)	33.05 (20-53)
Male – n (%)	12 (60%)	20 (62.5%)
Height – mean cm	169 (150-182)	169.3(151-187)
Weight - kg mean	67.25 (49.05-121.7)	60.7 (38.95-85.5)
BMI	25.8 (18-36.4)	21.02(16.9-28.37)
Sweat Chloride mmol/L	98.05 (56-113)	Not done
Smoker – n	0	0
Oxygen Supplementation	Nil	Nil
Exocrine Pancreatic Insufficiency – n	18	32
CF Diabetes Mellitus – n	1	15
CF Liver Disease – n	1	12
Fat Mass %	23.03 (4-42)	21.07 (2.4-41.1)
Genotype		
G551D/G551D	2	N/A
G551D/ df508	12	N/A
G551D/Other	G524X (2), V520F (1), Unknown (2)	N/A
df508/df508	N/A	32
Lung Function		
FEV1 % predicted mean	54.5 (20-99)	41.9 (24-95)
FVC % predicted mean	71.05 (40-96)	64.1 (38-107)
Baseline Cognition values		
MOCA score	27.6 (22-30)	27.5 (25-30)
Trail A – speed seconds	28.06 (23-36.9)	25.4 (12.3-38)
Trail B – speed seconds	Not done	50.4 (20-83.60)
Cogstate™ score	Not done	$9.02X10^{-17}$(-.95-0.80)

I MOCA

The MOCA score improved significantly at the open-label extension in the ivacaftor study, with the mean score improving from 27.6 ± 1.98 to 28.6 ± 1.88 ($p < 0.05$), out of a maximum score of 30. A treatment effect of this change was calculated as 0.95 ± 1.88 ($p < 0.05$).

MOCA score in the LUM/IVA Study also improved significantly from baseline to 12 months on treatment from 27.48 ± 2.18 to 29.05 ± 1.36 ($p < 0.01$) with a treatment effect of 1.57 ± 2.2 ($p < 0.01$). Baseline MOCA scores for both the ivacaftor and the LUM/IVA cohorts were above the clinical cut-off, i.e., > 26 points on a 30-point scale (Table 3) [24]. In the ivacaftor cohort 15% (n=3) of subjects scored below 26, improving to 10% (n=2) after 12 months. No treatment effect was seen within the placebo period compared to the active drug. In the LUM/IVA cohort10% (n=2) of subjects scored below 26, improving to 5% (n=1) at 12 months.

II Trail Making Test A and B

In the ivacaftor cohort, there was a trend towards improvement found in Trail A, with speed improvement from 28.06 ± 3.78 seconds to 25.12 ± 6.95 seconds ($p = 0.09$). There was a treatment effect during the placebo period in this cohort, (32.4 ± 7.6 to 23.2 ± 5.4, $p < 0.01$). On LUM/IVA, Trail A improved initially at the 6-month time point; however, at 12 months, this did not reach a significance 25.4 ± 7.56 to 22.24 ± 6.95 ($p = 0.06$). Trail B improved significantly at 12 months on treatment from 50.42 ± 16.44 to 39.25 ± 14.65 ($p < 0.01$). Trail A in both treatment groups and both Trail A and B in the LUM/IVA group were all within their age-matched normative ranges at baseline, Trail B improved to be outside (better) than the expected range (Tables 1 & 3).

Table 3: Baseline cognitive tests compared to normal range [21, 22, 24].

		Baseline	Normal range
Ivacaftor	MOCA score	27.6	>26
	Trail A - speed seconds	28.06	22.93-39.32
Combination	MOCA score	27.48	>26
	Trail A - speed seconds	25.40	22.93-31.78 (25)
	Trail B - speed seconds	50.42	48.97-63.76 (25)
	Cogstate™		
	ID - speed seconds	2.75	2.66-2.71 (28)
	Maze – n errors	49.47	40.88-55.7 (28)
	Shopping list - n correct	27.18	22.79-26.54 (28)
	One back speed	2.91	2.79-2.9 (28)

III Cogstate™

Performance on the Cogstate™ battery: Identification (ID), Groton Maze Test (GMT), International shopping list (ISL), and One Back (OB), is listed in (Table 1). During the Identification test, mean overall performance was below the age-matched normative speed range at baseline (Table 3) and worsened on LUM/IVA therapy at 12 months, increasing from 568.35 ± 105.45 log10 milliseconds to 632.12 ± 108.77 log_{10} milliseconds ($p < 0{\cdot}01$) and with a significantly lower score on this test 98.06 ± 5.88 log_{10} milliseconds falling to 94.47 ± 5.5 log_{10} milliseconds ($p < 0.05$).

In the Groton maze test, mean performance was within the age-matched normative range at baseline and improved significantly in scores 103.35 ± 11.9 to 107.29 ± 9 ($p < 0.05$), with the number of errors also falling (improving) from 49.47 ±31.12 to 39.47 ± 23.35 ($p < 0.05$) at 12 months on LUM/IVA. In the International Shopping List, mean performance at baseline was within the age-matched normative range. There was no improvement in the number of correct responses for the ISL; however, the duration of the test was significantly quicker improving from 262300.18 ± 44030.93 log_{10} milliseconds to 217093.06 ± 30243.4 log_{10} milliseconds ($p < 0.01$).

In the One Back card game, mean performance at baseline was below the age-matched normative range at baseline and improved significantly at 6 months in terms of both score 96.22 ± 5 log_{10} milliseconds to 100.1 ± 6.04 log_{10} milliseconds ($p < 0.05$) and speed, 818.57 ± 141.71 log_{10} milliseconds to 721.13 ± 138.05 log_{10} milliseconds ($p < 0.5$). Although not significant, after 12 months of treatment, the cohort did improve enough to be within the expected range (Table 3).

A combined cognition score was also calculated for the LUM/IVA cohort, taking into account all of the Cogstate™ domains as well as MOCA and TMT, observing the overall change in the individual. At 6 months, there was a 5.1% ± 8.63 improvement in this score which was significantly different from baseline ($p < 0.05$). The overall improvement of 6.20% ± 9.22 from baseline after 12 months on LUM/IVA therapy was also significant ($p < 0.05$).

Discussion

The cognitive domains assessed in both the ivacaftor and LUM/IVA studies showed promising results for gene-modulator therapy in CF when assessed using different measures, improving significantly after 12 months treatment when measured by the MOCA, TMT and by a combined cognitive score. Most prominent were improvements in executive function, incorporating inhibition and interference control, working memory and cognitive flexibility [25]. Aspects of executive function are assessed particularly in the Groton maze test, One Back card game, MOCA and Trail making tests. In all but the One Back game, performance on these measures improved significantly after 12 months of treatment with LUM/IVA. Improvements in total MOCA score were demonstrated in a second independent cohort as part of the ivacaftor study. It has been shown that improvements in executive function

correlates with better quality of life as well as physical health, mental abilities and competence in school and work and therefore, a significant improvement in executive function has wide implications for CF patients [25, 26].

In contrast, performance on tests measuring speed (TMT A and Identification) or verbal memory (shopping list errors) did not consistently improve with gene modifying therapy. As both groups of CF patients were largely within the normal range of performance on these measures at baseline, it is possible that ceiling effects may account for this lack of improvement.

Several limitations of this study should be considered. Due to the nature of the intervention and reasons for access to the study drug, the number of participants was low. This limited power overall and reduced capacity to include several baselines, uncontrolled covariates. For example, we were unable to incorporate level of education due to the low number of participants. Tombaugh (2004) reports that for TMT A and B age has a greater effect on the varience of results than education level, which was further reduced when results were entered hierarchically after age to less than 1% and 2%, respectively [21].

Practice effect of cognitive tests cannot be overlooked; however, these are less problematic given the relatively long follow-up period of 6 and 12 months. Similarly, by using a range of assessments to observe cognition, this confounder can hopefully be minimised when analysing an overall change. There was no placebo effect seen in MOCA in the ivacaftor study, however there appears to be one for Trail A at one month on placebo, which is consistent with the finding of Bartels *et al*. (2010), who found that increased frequency of cognitive testing was associated with higher practice effect and that longitudinal studies (up to a year) were less affected [27]. However, the crossover nature of the study accounted equally for the training effect in both active and placebo arms. There was no placebo comparison arm in the LUM/IVA study, however, the increased test-retest time intervals of six and 12 months minimise this confounder. A study in young healthy adults by Falleti *et al*. found that at one-month of practice effects of the Cogstate™ battery were not found [28].

Chronic inflammation and hyperglycaemia in CF are associated with cognitive decline; and while the prevalence of cystic fibrosis related diabetes (CFRD) may affect up to 50% of adults this could be a confounding factor in our study [15, 29]. However, with only one subject in the IVA study and twelve in the LUM/IVA study with CF-related diabetes, this cannot be proven in the current analysis.

While physical health and wellbeing have been shown to improve on CFTR modulator therapy, there is the possibility that these agents also contribute to improved cognition, particularly executive function [12]. This may be an indirect effect - exercise is also linked to the increased hippocampal size and has been linked to a reduced rate of age-related decline in memory [30]. However, with the knowledge that *CFTR* is expressed in the CNS, it is also possible that the changes seen are a direct effect on the channel itself, via a range of potential mechanisms: While *CFTR* has an unknown role in the brain, it can be presumed to act as an ion channel, potentially a neuromodulator and possibly interact with other CNS proteins. In addition, *CFTR* acts to control mitochondrial function, which is an important requisite for normal cognition [2]. A mutation in *CFTR* may therefore be expected to contribute to energy-dependent neuronal dysfunction. To date, this has not been studied extensively in CF, with few limited studies addressing this aspect.

To support the possibility of CFTR modulators having any direct effect on cognition, Schneider *et al*. suggest that IVA and LUM cross the blood-brain barrier and exert CNS activity, in part because of their lipophilic nature [17]. Ivacaftor and its metabolites have also been shown to have binding affinity to 5-hydroxytryptamine (5-HT; serotonin), suggesting anxiolytic properties and an effect on mood [17]. These effects were not tested directly in the current study but may also be a mediating mechanism for effects on cognition. With the known abundance of *CFTR* in the brain, a role of potentiation/correction of *CFTR* function in the CNS would therefore support our findings of improved neurocognitive function identified in this pilot study [5].

Conclusion

Further prospective randomized controlled studies involving larger cohorts of subjects on CFTR modulation therapy are needed to confirm any potential neurological role for IVA, LUM/IVA, and possibly the next generation of CFTR modulators in appropriate CF patients.

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Conflicts of Interest

John Wilson has received research grants and speaker fees from Vertex Pharmaceuticals Pty. Ltd. Tom Kotsimbos, Dominic Keating, Felicity Finlayson, Elyssa Williams and Brenda Button have been paid speaker fees by Vertex Pharmaceuticals Pty. Ltd. There are no other relationships or activities that could appear to have influenced the submitted work.

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