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## Paediatric Respiratory Reviews



## Review

## CFTR modulator therapies – Effect on life expectancy in people with cystic fibrosis

I.M. Balfour-Lynn\*, J.A. King

Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, UK

## Educational aims

The reader will be able:

- To understand long term effects of CFTR modulators in people with CF, focussing on life expectancy.
- To appreciate which complications of CF predict mortality and how CFTR modulators may affect them.

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## ABSTRACT

CFTR modulators have dramatically changed the clinical course of CF in those fortunate enough to receive them. Inevitably, randomised controlled trials during the development of these drugs are too short to use mortality as an outcome. Evidence for their effect on life expectancy are best gained from real world registry studies specifically looking at mortality, but these are only available for ivacaftor to date. Therefore, indirect evidence must be obtained by looking at outcomes known to affect mortality and seeing the effect of these drugs on those outcomes.

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## INTRODUCTION

For the last 8 years, drugs that target the basic defect in cystic fibrosis (CF) – the CF conductance regulator (CFTR) ion channel, have become available to a growing number of people with CF. Known collectively as CFTR modulators, they can either potentiate the activity of the CFTR channel that is at the epithelial cell surface, or correct the defect by allowing CFTR to reach the cell surface [1]. A number of such drugs are under development but only four are licenced to date. The principle potentiator is ivacaftor, which is either used on its own, or combined with a corrector such as lumacaftor (combined as Orkambi); tezacaftor (combined as Symkevi or Symdeko) or Elexacaftor (combined also with tezacaftor as Trikafta). There are numerous reviews of these drugs and this article will not present data from the various randomised controlled trials. Suffice to say that their rapid development is one of the most dramatic

breakthroughs in CF care, as we are no longer just treating the downstream effects – symptoms and complications.

Since CF was first recognised over 80 years ago, the improvement in life expectancy of people with CF has been a major medical achievement. In the UK, mortality rates decreased annually by 2% between 2006 and 2015, with median survival at birth in Phe508-del homozygotes calculated as 46 years for men and 41 years for women [2]. If mortality continues to drop at the same rate, this figure is suggested to improve to 65 years for men and 56 years for women [2]. Similarly, in the US where registry data were assessed from 2000 to 2010, mortality dropped by 1.8% per year during that period [3]. There are now more adults than children with CF, at least in developed countries, due to low mortality in children and increasing longevity in adults [4].

The US figures came from data that predated the era of CFTR modulator therapy, whilst the UK data included use of ivacaftor in just 5% of the patients for the latter 3 years, so cannot have had an appreciable effect on long term mortality figures. It is reasonable to speculate that these drugs will alter the natural history of the disease [5]. This article will present information on what is known about the effect on life expectancy, presenting both direct and indirect evidence.

\* Corresponding author at: Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK. Fax: +44 (0) 207 349 7754.

E-mail address: [i.balfourlynn@ic.ac.uk](mailto:i.balfourlynn@ic.ac.uk) (I.M. Balfour-Lynn).

## DIRECT EVIDENCE

Direct evidence is clearly more compelling. Whilst this could come from extending the phase 3 randomised controlled trials (RCTs), numbers are likely to be too small to detect differences in mortality, especially in children. There are phase 4 studies which are a regulated form of studying real world data, usually to pick up rarer adverse effects, and which used to be known as post-marketing surveillance. Then there are actual observational real world studies that need national patient registries to get high enough numbers to make the results meaningful. In addition, hypothetical modelling of the long term outcomes may be performed.

### Real world data

Real world data that gives information on mortality is only available for ivacaftor since it was the first drug to be licenced and became available in 2012. Even then that only allows a maximum of 8 years long term outcomes, although this is longer if patients who were in the initial RCTs are included, especially as the majority went into open label extensions. There are no published real world data assessing mortality yet on Orkambi, Symkevi, or Trikafta.

Bessonova et al., produced the first national registry analysis looking at disease modification by ivacaftor used for those with gating mutations for a single year (2014) [6]. It was a post-approval mandated pharmacovigilance study and six of the authors were from the company that produces ivacaftor. They compared 1256 ivacaftor-treated patients vs 6200 matched patients (with proven equivalent genotype severity) in the USA; and 411 treated patients vs 2069 untreated in the UK. In the US, there was a significantly lower risk of death (0.6% vs 1.6%) and lung transplantation (0.2% vs 1.1%). Trends were similar in the UK but did not reach significance presumably due to the smaller numbers; for risk of death it was 0.7% vs 1.4%, and for transplant 0.5% vs 0.9%. The study looked at the effect of ivacaftor treatment for a mean of 2 years in the US and 1.3 years in the UK, so to see a change in mortality in such a short period is remarkable.

The above study was continued and they recently reported results from their cross-sectional safety analysis with 5 years follow up in USA (2012–2016 inclusive), and 4 years in the UK (2013–2016 inclusive) [7]. The lower risk of death for those on ivacaftor that was noted in the first year was maintained, and similarly the risk of lung transplant.

### Modelling data

A forecasting US study, published in 2016, looked at outcomes and costs for ivacaftor used for patients with the p.Gly551Asp (formerly G551D) gating mutation [8]. Their model created a hypothetical cohort of 1000 patients comparing patients having usual CF care or CF care plus ivacaftor, with a non-CF population. Their main result was that ivacaftor was associated with an average of 18 additional years, and an 18% absolute decrease in the likelihood of a lung transplant. Because their model took patients starting at 25 years of age, one could speculate that figures would be even more encouraging since people are now starting ivacaftor aged 6 months. They made an interesting adjustment to their model, the assumption that after 2 years the efficacy halved, based on adherence challenges. This adjustment is not unreasonable given the data from a small study using electronic monitoring that showed an overall adherence to ivacaftor of 61% which decreased over time [9]. Stopping ivacaftor not only reverses the gains, but

a case series of 3 adults showed a withdrawal syndrome with rapid deterioration in lung function and a pulmonary exacerbation [10].

There has also been a study modelling survival for patients homozygous for Phe508del who are taking Orkambi, with two authors from the drug company [11]. Orkambi is currently available from 2 years of age, they modelled starting at various ages and assumed life time use, comparing with standard care. They stated that multiple analyses indicate that lung function, pulmonary exacerbations and nutritional status predict survival so based their modelling on these data from the RCTs. Overall incremental median survival was predicted to be 8 years, and for those starting at age 6 years it was 23 years; and starting at age 12 years it was 18 extra years. Given the level of benefit found in the original trials, this sounds somewhat optimistic, and it will be interesting to see if real world data back this up when available. The same group who created the forecasting study for ivacaftor [8] used that model to study Orkambi; they found its use was associated with an extra 3 life-years compared to usual care alone using the assumption that efficacy is halved after 2 years due to adherence issues, but if Orkambi retained full efficacy, that was raised to 8 years [12].

## INDIRECT EVIDENCE

Indirect evidence comes from research that does not include mortality as an outcome, but looks at other outcomes in CF that are known to effect life expectancy. Improvement in these surrogate markers may suggest that life expectancy will change also, but it is an assumption rather than proof. A 5 year survivorship model has been produced using the US registry; they analysed data from nearly 6000 patients and validated it on a further almost 6000 [13]. Although published nearly 20 year ago, it is likely that most of the key features identified are still relevant now. These are outlined below, with a few additions (table).

### Prognostic outcomes with CFTR modulator data

- Lung function
  - Absolute FEV<sub>1</sub>
  - Decline in FEV<sub>1</sub>
- Exercise testing
- Pulmonary exacerbations
- Airway microbiology – *B. cepacia* complex
- Nutritional status
- Pancreatic insufficiency
- CF liver disease
- CF-related diabetes
- Mental health
- Quality of life

### Lung function

Multiple analyses have indicated that FEV<sub>1</sub> (forced expiratory volume in 1 s) predicts survival in CF and there are many references in the Rubin modelling paper [11]. Indeed, it remains one of the cornerstones of decision-making in lung transplant assessment. Data taken from RCTs with FEV<sub>1</sub> as a primary outcome are subject to an additional 'trial effect' due to being closely monitored in a trial, so, longer term registry data are preferable. Additionally, rate of decline in FEV<sub>1</sub> is associated with life expectancy [14], and in terms of therapeutic interventions, is likely to be a better predictor of change in mortality than an absolute change. However, RCTs are rarely long enough to study rate of decline with any certainty.

Sawicki et al. studied patients with p.Gly551Asp mutation on ivacaftor, combining trial and registry data over 3 years [15]. The annual estimated rate of decline in FEV<sub>1</sub> was compared with

homozygous Phe508del patients, and was slowed by almost a half. A note of caution is that comparison of trial patients (both phase 3 and open label extensions) with real world registry patients not in a trial, may give an exaggerated improvement due to the trial effect mentioned above. The 5 year US and UK registry follow up of ivacaftor that reported mortality data [7], separately reported lung function data, with 7 authors from the pharmaceutical company [16]. They found ivacaftor-treated patients had better preserved lung function, although following the initial improvement at year 1, both groups declined over the subsequent 4 years. A relatively small registry study from Ireland, studying 80 patients with a gating mutation who were taking ivacaftor, found change in lung function over a 3 year period was age dependent following the initial improvement seen when starting the therapy [17]. There was an improvement in the under 12s; it was stable in 12–17 year olds; and declined in adults aged 18 and above, however there was no comparator group used.

As regards Orkambi, there has been a 96 week open label extension of the initial trials (PROGRESS) comparing a matched registry cohort [18]. They reported a 42% slower rate of lung function decline, but again caution over conclusions when comparing trial with registry patients is warranted. There is an ongoing observational study (PROSPECT) that has not yet been published. There has been a real life post-approval assessment of Orkambi for a one year period in 47 centres in France, that demonstrated an absolute increase in lung function, but a surprisingly high discontinuation rate (18%) [19].

#### Lung clearance index

Lung clearance index (LCI), is an important trial outcome in younger children, but has not been studied long term, which is not surprising given it is not as readily available as standard spirometry, and is not measured in every clinic visit. Currently, values are not routinely put onto registries and we do not even know how well these measures are associated with life expectancy.

#### Exercise testing

An old study of laboratory exercise testing in children and adults showed that higher levels of aerobic fitness measured by peak oxygen consumption ( $VO_{2peak}$ ) were associated with a lower risk of dying [20]. Extensive exercise testing is not carried out routinely and does not form part of registry data. However, one small crossover study on ivacaftor in p.Gly551Asp patients did not show change in maximal oxygen consumption ( $VO_{2max}$ ) nor minute ventilation after cardiopulmonary exercise testing, despite a significant rise in  $FEV_1$ ; although it was only over one month [21].

#### Pulmonary exacerbations

Pulmonary exacerbation rate is another important predictor of survival; the 5 year survivorship model found that each acute exacerbation had an unexpectedly large negative impact [13]. A single large centre in Canada found that adults with >2 exacerbations per year had an increased risk of death or transplantation over the 3 year study [22]. A US registry study found that 3 months following an acute exacerbation, lung function had not recovered to the baseline prior to the exacerbation in 25% patients; the risk was associated with a number of factors [23]. Furthermore, the annual rate of decline in  $FEV_1$  is higher in those with  $\geq 1$  exacerbation compared to none, and particularly if there is less than 6 months between exacerbations [24].

In the real world registry study of ivacaftor, pulmonary exacerbation rate was 28% in the treatment group compared to 43% in the comparator group, and we know mortality was reduced in the for-

mer, although exacerbations would not have been the only factor [6]. The 5 year study extension, found that the proportion of patients having a pulmonary exacerbation fell from 38% to 26% in the ivacaftor group, whilst it increased from 33% to 44% in the comparator group [16]. It is hard to believe this will not affect life expectancy.

The reduction in exacerbation rate found in the Orkambi RCTs was maintained in the open label PROGRESS extension, but there is no registry data yet, and there might not be, as the largest user – the US, will have converted most people to Trikafta (age permitting) [18].

#### Airway microbiology

Certain pathogens have a particularly deleterious effects on the lungs, for example *Burkholderia cepacia* complex, and *Mycobacterium abscessus*. The 5 years survivorship model found that infection with *B. cepacia* had the largest effect of any model variable for predicting survival [13], although that may well have changed since the 1993 cohort, with newer antibiotics available. Patients with *B. cepacia* complex tend to be excluded from RCTs so there is not much data. However, a UK registry study (with a comparator group) of ivacaftor usage in 276 patients aged 6 years and above, found over a 6 year period, an early and sustained reduction in *Pseudomonas aeruginosa* (increased clearance and reduced acquisition), a reduction in *Aspergillus* species, a smaller reduction in *Staphylococcus aureus*, but a less than 1% non-significant change in *B. cepacia* complex [25]. The US G551D Observational study (GOAL) was an observational registry study of ivacaftor use in 150 patients aged 6 and above; they also found no change in prevalence of *B. cepacia* complex [26]. The number of patients with *B. cepacia* complex are so low that perhaps it is not too surprising that significant changes are not detected.

#### Nutritional status

Many studies have shown nutritional status predicts survival in CF and again there are many references in the Rubin et al modelling paper [11]. The 5 year survivorship study found that weight for age z score substantially affected long term outcomes [13]. Body mass index (BMI) is one of the primary outcomes in most modulator RCTs and is easy to measure.

The Sawicki et al. 3 year data on ivacaftor for p.Gly551Asp also showed an improvement in BMI and weight for age z scores that was maintained, but although significant, the differences between the treated and comparator groups were quite small [15]. The US and UK registry follow up of ivacaftor found an improvement over 5 years in BMI of 2.4 kg/m<sup>2</sup> compared to 1.6 kg/m<sup>2</sup> in the US, and 1.9 kg/m<sup>2</sup> vs 0.9 kg/m<sup>2</sup> in the UK, so again, encouraging but relatively small changes [16]. For Orkambi, the change in BMI was just under 1 kg/m<sup>2</sup> in the open extension [18] and French real world 1 year data [19].

More intriguing will be the longer follow up from children on ivacaftor for gating mutations aged under 6 years, who are having a varying degree of restoration of pancreatic function marked by an increase in faecal elastase [27–29]. Pancreatic status is an important predictor of survival [13]; with pancreatic sufficient patients generally doing better. Some of that effect though is likely due to certain genotypes associated with pancreatic sufficiency causing milder disease in general.

#### CF liver disease (CFLD)

Whilst liver involvement is common in CF, fortunately significant disease with severe cirrhosis and portal hypertension is relatively infrequent. Some have not shown CFLD to be associated with

increased mortality [30]. However, an Irish study of 84 children with matched controls, which reviewed them 10 years later, found CFLD with portal hypertension was an independent risk factor for all-cause mortality with almost 3 times the risk of death compared to those without CFLD [31].

There is not much data on the potential beneficial effects of CFTR modulators on CFLD, although raised liver enzymes is a recognised adverse effect. Ivacaftor has been found to partially restore bile acid homeostasis [32], and Orkambi reduced hepatic steatosis assessed by MRI hepatic fat fraction [33]. The Bessonova early real world data on ivacaftor did find a lower report of hepatobiliary complications, that included gallstones, liver disease, cirrhosis and its complications (varices, splenomegaly, ascites), and steatosis (5% vs 8% in US, 22% vs 28% in UK); the reason figures are so much higher in the UK is that its registry definition included abnormal liver enzymes [6]. A direct ivacaftor effect could not be proven though.

#### *CF-related diabetes (CFRD)*

CFRD is another CF complication that is associated with increased mortality, particularly in females [13,34]. There have been a number of small studies, reviewed by Sergeev et al [35], including two that have shown an improvement in insulin secretion after 1 month [36] and 4 months [37] of ivacaftor therapy. The ivacaftor real world US and UK registry study showed a reduced prevalence of CFRD in the ivacaftor group (30% vs 40% in US, and 21% vs 29% in UK) [6]. However, the study did not account for potential differences in CFRD prevalence before starting the ivacaftor [35]. Nevertheless, these trends persisted in the 5 year follow up, although did not reach significance [16].

Orkambi taken for a year led to an improvement in glucose metabolism in a group of 40 patients who had either glucose intolerance (78%) or CFRD (22%) [38]. A small study that used continuous glucose monitoring as well as oral glucose tests in 9 children on Orkambi (pre and a median of 29 weeks after) found no improvement in glucose metabolism although the boys showed lower glycaemic variability [39]. These results are mixed but encouraging, however, what we need to know is whether starting effective CFTR modulators early in life will prevent development of CFRD in the first place, as that really would affect life expectancy.

#### *Mental health and quality of life*

Numerous studies have shown an increase in rates of anxiety and depression amongst children and adults with CF, as well as parent caregivers [40]. Psychological symptoms have been associated with decreased lung function, lower BMI, worse adherence, worse health-related quality of life and more frequent hospitalisation [40]. These would all suggest that mental health issues would affect life expectancy. The real world registry study of ivacaftor found a significantly lower prevalence of depression in the US patients (14% vs 17%) and a non-significant lower level in the UK (4.4% vs 5.9%), in those taking ivacaftor [6]. Conversely, there have been reports in patients starting Orkambi of increased severity or new onset depression, or bipolar disorder associated with suicidal ideation [35]. Drug interactions with psychotropic medication may be responsible those on pre-existing therapy, but not new cases.

Patient-reported outcomes, usually a health-related quality of life score, are part of most phase 3 RCTs and were uniformly shown to improve with CFTR modulators. Real world data does not exist as quality of life scores are not routine in clinical practise so are not routinely documented in national registries. The US G551D Observational study (GOAL) of ivacaftor found significant improvements in all measures of quality of life, including the respiratory domain of the CFQ-R (CF Questionnaire-Revised) score [41]. The

STRIVE study of ivacaftor over 48 weeks found treatment effect favoured ivacaftor in terms of respiratory symptoms, physical and social functioning, health perceptions and vitality measured by CFQ-R [42]. A multinational real world cross sectional survey comparing use of ivacaftor for p.Gly551Asp with standard care for homozygous Phe508del patients, found significantly better scores using CFQ-R and EQ-5D-5L (EuroQoL 5-dimensions 5-level) questionnaires in the ivacaftor group who had taken it for a mean of 22 months [43]. One can assume therefore, that this is another way CFTR modulators can impact life expectancy, and also QALYs (quality-adjusted life years).

### **CONSEQUENCES OF INCREASED LIFE EXPECTANCY**

Assuming life expectancy truly increases there will be a number of consequences for the CF population and health services.

#### *Ageing*

Even now, when CF adults have been brought up in the era before CFTR modulators, due to many factors, they are living longer, and death in childhood is an uncommon event [44,45]. An ageing population of people with CF is almost a certainty and this will bring with it several medical complications [46,47]. Particular conditions, that are age-related, include CFRD, bone disease and arthropathy, although hopefully the CFTR modulators will change that pattern. Obesity is a potential issue since CFTR modulators lead to increased weight and the standard diets will need to be modified [5]. Importantly, there is a known increase risk of cancer in people with CF, particularly of the gastro-intestinal tract (including the biliary tract and pancreas), as well as lymphoid leukaemia and testicular cancer [48,49]. The effect of CFTR modulators on cancer risk is unknown [5]. However, for now, one must assume that this life time risk will increase with further ageing and screening programmes that are already recommended for colorectal cancer, may need to be broadened. Additionally, those who advocate regular chest CT scanning may need to rethink, even with the modern low radiation CT scanning protocols.

#### *Need for more adult units*

There is already a shortage of specialist adult CF units and appropriately-trained medical, nursing and allied health professionals, with many centres in Europe relying on support from paediatric colleagues [50]. Projections suggest numbers will expand greatly, and even more so since the advent of CFTR modulator therapy, making the situation worse [51,52]. Although the CF population will be healthier, they will still need close follow-up for reasons cited above, and careful monitoring of medications. Manpower planning and increased specialist training in CF are urgently needed [52,53]. New ways of working will be necessary, including perhaps network shared care [52]; and increased use of telemedicine and videoconferencing (which has had a sudden surge in its use during the Covid-19 pandemic).

#### *Financial considerations*

CFTR modulators are extraordinarily expensive, and likely to be beyond the reach for many health services across the globe. This is certainly a huge problem for lower and middle income countries, as well as national health services in countries outside the US. Of course, there will be potential savings for health services in terms of hospital admissions, and other drug costs – assuming research proves they can be withdrawn. There may be a reduction in price once more than one company are producing effective drugs. Drugs

coming off patent and production of generic versions may help in the future, but there is no guarantee that the generic drugs will be much cheaper. If one considers Trikafta costs \$311,503 per year per patient in the USA, and that in time it will be started in 2 year olds (or younger even), then if that toddler lives until 75 years, the cost of that one drug alone for that one person will be almost \$23 million. Multiply that by the potential 90% of patients eligible for these drugs and clearly something needs to change.

## CONCLUSIONS

Most of the long term data that informs mortality, relates to ivacaftor used in relatively few patients. Whilst there is some indirect data for Orkambi, it is not as effective as ivacaftor in those with the relevant mutations. The real hope for the majority of people with CF is the newer triple therapy – Trikafta. It would be extremely surprising if life expectancy was not significantly improved when, and if, this drug becomes widely available, especially since trial data suggests the outcomes are as good as those with ivacaftor. It is likely that the earlier these drugs are started the better, perhaps even in utero, but of course, we do not yet know about long term safety. Increasingly though, it looks like CF will no longer be a life-limiting disease.

## DIRECTIONS FOR FUTURE RESEARCH

- Real world mortality studies of all CFTR modulators, not just ivacaftor.
- To ascertain whether long term use of these drugs is safe.
- To understand what level of adherence will be achieved in the long term.

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