Can clinical benefits of modulators effectively 'modulate' adherence in people with CF?

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Cystic fibrosis (CF) is a progressive, life-limiting genetic disease caused by a dysfunctional CF transmembrane conductance regulator (CFTR) protein that leads to mucus clearance abnormalities, the development of chronic endobronchial infections and progressive, irreversible lung damage. Historically, treatments for CF have largely been supportive in nature and have focused on symptomatic improvement from the many CF-related disease manifestations, including pulmonary, gastrointestinal and sinus-related morbidities. The use of acute and chronic medications to address these disease-related complications has undoubtedly improved the lives of people with CF (PwCF) and extended life expectancy.

The approval of ivacaftor by the US Food and Drug Administration on 31 January 2012 for PwCF 6 years and older with a G551D mutation has heralded in a new era of CF care. For the first time, a CF therapy (termed CFTR modulator) was developed to target the underlying CFTR protein defect itself. Since its approval, several other CFTR modulators have been deployed in the clinical arena; the most recent (and arguably the most effective) of which is elexacaftor/tezacaftor/ivacaftor, a CFTR modulator currently approved for all PwCF 12 years and older with at least once copy of the Phe508del mutation.

While the approval of CFTR modulators has revolutionised the care of PwCF and might even improve life expectancy, there remains a number of potential barriers to CFTR modulator adherence, including cost, perceived medication benefit, delays in prior authorisations, decreased access to care and individual factors (depression and anxiety). For example, medication adherence rates for PwCF approximate 50% and range between 35%–75% depending on age, medication type and population tested.[1] Interestingly, lung transplant recipients who rely on chronic immunosuppressive therapies to reduce the risk of transplant rejection have imperfect medication adherence rates, with up to a quarter of transplant recipients self-reporting immunosuppressive medication non-adherence.[2] Based on these data, maintaining and improving medication adherence in the face of a chronic disease can be quite challenging. To make matters worse, studies in PwCF have found an association between lower medication adherence rates and worse clinical outcomes, including lower baseline lung function and an increase in the number of pulmonary exacerbations requiring intravenous antibiotic therapy.[3] Less is known, however, about CFTR modulator adherence rates due to their relatively recent approval and it is unclear if the clinical benefits of CFTR modulators seen in clinical trials will translate to improved medication adherence.

In this issue of *Thorax*, Dr Mitchell and colleagues sought to both evaluate the long-term impact of ivacaftor on a cohort of PwCF but also to determine adherence to this CFTR modulator over time. They conducted a 5-year single centre, retrospective cohort study of 35 PwCF (mean age: 29 years) carrying the *Gly551Asp* mutation who received ivacaftor at their CF centre in Manchester, England.[4] Clinical and demographic data were collected starting 2 years prior to ivacaftor initiation and up to 5 years after starting the medication. Ivacaftor adherence was assessed using the medicine possession ratio (MPR) that compares days of treatment received to days of treatment prescribed. These data were available to the investigators since ivacaftor was delivered by homecare delivery companies who monitor ivacaftor stock and fulfil orders only when additional medication is needed.

Following treatment initiation, PwCF taking ivacaftor had an overall mean absolute improvement in baseline forced expiratory volume in one second (FEV_1) of 9.6% (SE: ±1.59) at 6 months. In addition, mean body mass index for PwCF on ivacaftor increased yearly over the study period and, when compared with the pre-ivacaftor period, fewer intravenous antibiotic treatment days were recorded. Interestingly, the overall rate of FEV_1 decline over the 5-year study period (1.82% (SE: ±0.45)) was not different when compared with the 2 years prior to ivacaftor initiation (1.57% (SE: ±1.31)). Medication adherence was quite high within 3 months of ivacaftor prescription (mean MPR was 99.6% (SE: ±0.3)) but declined yearly at a rate of 2.5% (SE: ±0.9) and at 60 months had decreased to 87.5% (SE: ±4.5). A higher overall MPR was associated with a greater sustained FEV_1 improvement from baseline at 60 months and a reduced yearly rate of FEV_1 decline over the 5-year study period.

Important strengths of this study include the use of 'real-world' data and a follow-up period that was longer than the original clinical trial extension studies. While MPR is imperfect, the investigators took advantage of a unique opportunity to more objectively assess medication adherence (rather than by patient's report alone) and this study is one of the first of this size to report long-term ivacaftor adherence data. Results from this study add to the growing body of evidence that ivacaftor can rapidly improve lung function among PwCF. While there was no significant difference overall in the rate of FEV_1 decline pre-ivacaftor to post-ivacaftor initiation, a higher MPR was associated with a slower FEV_1 decline. One possible explanation for the overall lack of change in the slope of FEV_1 decline seen in this study might be the reduced use of other chronic maintenance therapies and an important limitation to this study is that adherence to these chronic therapies was not measured.

Importantly, while medication adherence was significantly higher in this study when compared with prior adherence studies, adherence did decrease over time which (when coupled with improved clinical outcomes seen among PwCF with higher adherence) is concerning. These data can likely be extrapolated to elexacaftor/tezacaftor/ivacaftor, and thus strategies targeting improved medication adherence are essential to maximise the benefits of CFTR modulators in PwCF. A survey of CF care centres found that only 64% of providers discussed treatment adherence at each visit and fewer than 10% used an objective assessment of adherence.[5] Thus, adherence barriers must be explored frequently and acted

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on by CF care teams in a timely fashion. While interventions for chronic diseases such as asthma have been shown to improve adherence,[6] thus far studies targeting adherence in CF have been less successful.[7] Behavioural strategies, including habit formation and routinisation of therapies, are one potential strategy to improve treatment adherence.[8] Future studies should consider taking advantage of existing quality improvement collaborations within and among CF care centres to rapidly trial small-scale interventions and quickly identify areas and strategies with the most potential to enact adherence changes. Until a more curative therapy (gene therapy?) becomes available, treatment adherence will remain an issue CF care teams must focus on to improve clinical outcomes among PwCF.

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