Tezacaftor-ivacaftor use in routine care of adults with cystic fibrosis: a medicine use evaluation

Iona Paterson ,[1] Chris Johnson,[2] Gordon MacGregor[3]

[1]Pharmacy, Queen Elizabeth University Hospital Campus, Glasgow, UK
[2]Pharmacy Services, NHS Greater Glasgow and Clyde Primary Care Division, Glasgow, UK
[3]Department of Respiratory Medicine, Queen Elizabeth University Hospital Campus, Glasgow, UK

Correspondence to
Iona Paterson, Pharmacy, Queen Elizabeth University Hospital Campus, Glasgow G51 4TF, UK; iona.paterson@ggc.scot.nhs.uk

Received 30 December 2020
Accepted 1 June 2021
Published Online First 8 June 2021

EAHP Statement 4: Clinical Pharmacy Services.

ABSTRACT

Objectives Cystic fibrosis is a devastating life-limiting genetic condition characterised by a progressive decline in lung function, respiratory infections and premature death. Tezacaftor-ivacaftor is a combined cystic fibrosis transmembrane conductance regulator (CFTR) modulator that targets the underlying cause of the disease. This study aimed to assess the impact of tezacaftor-ivacaftor use in routine clinical practice for adults with cystic fibrosis.

Methods A retrospective observational longitudinal cohort study design was applied to examine the clinical effect of tezacaftor-ivacaftor in routine practice in the West of Scotland Adult Cystic Fibrosis Unit. Adults receiving tezacaftor-ivacaftor for at least 4 weeks were included in this medicine use evaluation.
A standardised data form was used to collect patient-level data: demographics, genotype, complications of cystic fibrosis, medicine access process. Fifty-two weeks pre and post tezacaftor-ivacaftor initiation data: lung function, body mass index (BMI), days spent in hospital, days receiving antibiotic treatment for respiratory exacerbations. Anonymised data were collated and analysed using SPSS V.26.

Results Of 121 potential patients, 45 received treatment with tezacaftor-ivacaftor; median age 30 years (range 17–64) at initiation, 56% were male, 76% were deemed to be homozygote and 41 patients continued treatment for at least 52 weeks. There was no significant change in % predicted FEV_1; median difference 0 (IQR −3 to 6). There was a significant improvement in BMI, mean 0.6 kg/m^2 (95% CI 0.2 to 1.0), as well as a median 4 (IQR −17 to 0) day reduction in days in hospital and 21 (IQR −42 to 0) day reduction in days receiving antibiotics.

Conclusions The use of tezacaftor-ivacaftor in routine practice for people with cystic fibrosis was associated with improvements in weight, as well as reducing the number of days people needed to spend in hospital and receive antibiotics.

INTRODUCTION

Cystic fibrosis is a devastating genetic life-limiting condition, with more than half of sufferers dying before the age of 40.[1] More than 80 000 people around the world are known to have cystic fibrosis, with approximately 10 600 of those patients residing in the UK.[2 3]

Cystic fibrosis is an inherited autosomal recessive disease characterised by a slow progressive decline in lung function and repeated respiratory infections, caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein.[3] These mutations cause deficiencies in CFTR function which results in insufficient chloride exchange across epithelial surfaces, increasing sodium and water reabsorption, and subsequently increasing mucous viscosity in the biliary-hepatic system, pancreas, intestines and lungs.[2 3] As with other genetic disorders, the severity of illness varies according to which CFTR genetic mutation patients have. Phe508del mutation is the most common in Europe, affecting 40% of patients with cystic fibrosis; having two copies of Phe508del (homozygous) leads to more severe and rapidly progressing disease while those with one copy of Phe508del (heterozygous) experience less severe illness.[2 4]

As respiratory failure and chronic progressive pulmonary disease are the main cause of morbidity and mortality in cystic fibrosis, the main stay of treatment aims to prevent and manage respiratory infections in an effort to maintain lung function.[5] This requires an integrated multidisciplinary team approach to care involving a range of non-pharmacological and pharmacological support and services.[5 6] While treatment and management of the multiple body systems affected require chronic supportive medication such as long-term antibiotics, fat-soluble vitamins, mucolytics and pancreatic enzymes, respiratory infections require treatment with antibiotics. The respiratory exacerbations usually require 14 days of treatment with intravenous and/or oral antibiotics, requiring some patients to be admitted to hospital for the full 14 days, while others are trained to self-administer their intravenous antibiotics at home.[5 6] This can and does vary however with an individual's exacerbation and clinical condition which may require hospital admission. Current treatment strategies are limited, as they do not address the underlying aetiology of cystic fibrosis but aim to abate and slow the disease.

CFTR modulators target the dysfunctional CFTR protein and are the first class of medicines to act to potentiate or correct its actions. The first to market in North America, Europe and Australasia was ivacaftor in 2012, a CFTR potentiator which increases the probability of the CFTR channel opening at the cell surface allowing enhanced ion transport and reducing mucus viscosity.[7] Then the corrector lumacaftor was developed, which increases the amount of CFTR protein at the cell surface to enable improved chloride ion transport.[8] Both modulators were combined in one product, lumacaftor-ivacaftor, which has been shown to improve lung function and nutritional status, and to reduce respiratory exacerbations, therefore demonstrating cystic fibrosis disease-modifying effects.[9 10] Unfortunately, lumacaftor-ivacaftor is only effective in homozygous Phe508del patients, and its use is

To cite: Paterson I, Johnson C, MacGregor G. *Eur J Hosp Pharm* 2023;**30**:142–146.

limited by adverse drug effects and multiple drug–drug interactions.[8 11 12]

More recently, the CFTR potentiator ivacaftor was combined with a newer corrector tezacaftor and licensed in 2018.[13] Tezacaftor-ivacaftor is indicated to treat a range of patients who are either homozygous for the Phe508del mutation or heterozygous for the Phe508del mutation plus a residual function mutation.[13] The EVOLVE (VX14-661-106) and EXPAND (VX14-661-108) clinical trials have shown that treatment with tezacaftor-ivacaftor achieved significant improvements in lung function and reduced respiratory exacerbations,[2 14] as well as having fewer drug–drug interactions and adverse drug effects than lumacaftor-ivacaftor. As the regulatory studies were conducted in a clinical trial environment, this study aimed to assess the impact of tezacaftor-ivacaftor use in routine clinical practice for adults with cystic fibrosis: primarily, the effect of tezacaftor-ivacaftor on lung function and weight; secondarily, the effect on the number of inpatient hospital days and antibiotic treatment days for respiratory exacerbations of cystic fibrosis.

METHOD

Ethical opinion was sought from the West of Scotland Research Ethics Service on the use of anonymised patient-level data for the study. The study was considered to be service evaluation and therefore did not require research ethics approval; however, Caldicott Guardian approval was sought and granted by NHS Greater Glasgow and Clyde (NHSGGC) Caldicott Guardian.

A retrospective observational longitudinal cohort study design was applied to examine the clinical effect of tezacaftor-ivacaftor in routine practice.

The UK's National Health Service (NHS) is taxpayer funded and devolved to the national assemblies and parliaments in the home nations. The NHS in Scotland is organised into 14 regional health boards serving a population of 5.3 million people, living in highly rural (remote island communities) to highly urbanised areas with large variations in socioeconomic deprivation. The West of Scotland Adult Cystic Fibrosis Unit is the largest in Scotland and covers a diverse population of patients from 11 different regional health board areas, including highly urbanised as well as remote islands and rural areas. The unit currently cares for 289 patients ≥16 years old with cystic fibrosis.

The Scottish Medicines Consortium (SMC) is the national source of advice on the clinical and cost-effectiveness of all new medicines for NHS Scotland. In August 2019, SMC was unable to accept tezacaftor-ivacaftor for the treatment of cystic fibrosis for patients aged 12 years and older, due to uncertainties regarding the cost to benefit ratio of the medicine.[15] In September 2019, however, the Scottish Government announced that a pricing agreement had been reached with the manufacturer in order to allow clinicians in cystic fibrosis specialist treatment centres to prescribe tezacaftor-ivacaftor to patients who they considered would benefit from its use.[16] This agreement has an initial duration of 5 years, during which the manufacturer has undertaken to collect data on clinical outcomes experienced by patients prescribed tezacaftor-ivacaftor. Prior to the Scottish Government agreement, tezacaftor-ivacaftor could be accessed for patients via either: (1) the manufacturer's 2017 compassionate access scheme for patients meeting specific inclusion criteria where predicted forced expiratory volume in one second (FEV_1) is <40%,[17] or (2) once it received its marketing authorisation in December 2018, via the Peer Approved Clinical System Tier 2 (PACS2) non-formulary process. This allows clinicians to make individual patient-specific requests and gain approval to use medicines that are licensed for use but are 'not recommended by SMC', are 'outwith SMC restrictions' or the SMC is yet to issue advice.[18] Patients accessing tezacaftor-ivacaftor via the manufacturer's compassionate scheme received their medicines from the hospital pharmacy, whereas patients receiving access via PACS2 had their tezacaftor-ivacaftor delivered to their home via a Homecare company.

While EVOLVE and EXPAND assessed the primary measure of changes in FEV_1 from day 15 and week 4, and demonstrated short-term effects at 24 and 8 weeks, respectively,[2 14] we were interested in assessing longer-term effects in routine practice, and considered 52 weeks of treatment appropriate due to the potentially small number of patients that received tezacaftor-ivacaftor due to its restricted use. This medicine use evaluation therefore included patient-level data for adults who had received tezacaftor-ivacaftor for 4 weeks or more to assess tolerability.

The West of Scotland Adult Cystic Fibrosis Unit pharmacy database was used to identify patients for inclusion, as it contained data for all patients attending the unit and prescribed tezacaftor-ivacaftor from when it first became available in 2017. A standardised data collection form was used to collect patient-level clinical information from the unit's electronic and clinical information systems for the 52 weeks before and after starting tezacaftor-ivacaftor. Tezacaftor-ivacaftor efficacy was assessed using measures previously used in randomised controlled trials.[2 14]

Individual patient-level data captured using the standardised form included tezacaftor-ivacaftor start date; age at initiation; gender; residential postcode to allow mapping of Scottish Index of Multiple Deprivation (SIMD) codes; genotype (homozygous or heterozygous); cystic fibrosis–related comorbidities, such as diabetes. Data were also captured for FEV_1 percentage predicted; actual weight (kg); body mass index (BMI); number of inpatient days; number of antibiotic days; and number of medicines received, for the 52 weeks before and after tezacaftor-ivacaftor initiation.[2 12 19]

Patient-level data were collated and checked by two data collectors (IP and DC) using Microsoft Excel. Anonymised data were then analysed using the Statistical Package for Social Scientists (SPSS) V.26. Changes in measures before and after tezacaftor-ivacaftor initiation were assessed. First for the total cohort, intention-to-treat analysis using last observation carried forward, as defined by Cochrane,[20] was used to assess impact of treatment for all patients completing 4 weeks or more of treatment as per EVOLVE and EXPAND studies.[2 14] Further subgroup analyses of effects for homozygous patients were assessed. Due to the small number of heterozygous patients identified in this service evaluation, further analysis was considered inappropriate. Parametric and non-parametric statistical tests were applied where appropriate as guided by data viability. In particular, where continuous data were non-normally distributed and remained so after transformation appropriate, non-parametric tests were applied.

RESULTS

Two hundred and eighty-nine adult patients with cystic fibrosis received support from the West of Scotland Adult Cystic Fibrosis Unit at the time of data collection, with 98 (34%) patients being homozygous and 191 (66%) being heterozygous. In total, 121 (42%) of all patients were suitable for treatment with tezacaftor-ivacaftor based on genotype; however, not all patients were eligible for tezacaftor-ivacaftor due to manufacturer and PACS2 access restrictions, as outlined above.

In total, 37% (45 of 121) of potentially suitable patients received treatment with tezacaftor-ivacaftor for ≥4 weeks (table 1). At

Table 1 Baseline demographics and characteristics

At initiation	Homozygote (n=34)	Total (n=45)
Age, years median (range), years	29 (18–64)	30 (17–64)
Gender, male (%)	19 (56)	25 (56)
Cystic fibrosis–related comorbidities (%)		
Pancreatic insufficiency	34 (100)	37 (82)
Gastro-oesophageal reflux disease	19 (56)	21 (47)
Diabetes mellitus	18 (53)	18 (40)
Distal interstitial obstruction syndrome	13 (38)	17 (38)
Sinusitis	7 (21)	11 (24)
Liver insufficiency	9 (26)	9 (20)
Arthropathy	5 (15)	6 (13)
52 weeks preinitiation		
Weight, kg, mean±SD (range)*	60.7±10.6 (34.7–84.9)	62.3±10.7 (34.7–84.9)
BMI, kg/m^2, mean±SD (range)*	21.3±2.7 (15.0–27.4)	21.8±2.8 (15.0–27.7)
Days in hospital, median (range)*	14 (0–81)	13 (0–81)
Days receiving antibiotics, median (range)	56 (0–144)	56 (0–144)
FEV_1 (%), median (range)	45.0 (17.0–83.0)	46.0 (17.0–83.0)
Number of prescribed medicines, mean±SD (range)	13±5 (7–24)	12±5 (3–24)
Accessed CFTR modulator, (%)		
PACS2	24 (71)	33 (73)
Compassionate	10 (29)	12 (27)

CFTR, cystic fibrosis transmembrane conductance regulator; FEV_1, predicted forced expiratory volume in 1 second; PACS2, Peer Approved Clinical System Tier 2.

tezacaftor-ivacaftor initiation, patients' median age was 30 (17 to 64) years, mainly male (56%) and predominantly homozygous genotype (76%). The cohort were evenly distributed across SIMD quintiles. Four patients discontinued treatment within the 52 weeks' follow-up period: two started a clinical trial; one switched to ivacaftor-tezacaftor-elexacaftor; and one died. These four patients had a median age of 27 (range 18–36) years, were homozygous, predominantly male and continued treatment for median of 37 (19–40) weeks.

Primarily, tezacaftor-ivacaftor use was associated with a mean increase of 1.8 kg (95% CI=0.7 to 2.8 kg, p=0.002) in weight; increasing BMI by a mean of 0.6 (95% CI 0.2 to 1.0, p=0.003) kg/m^2. However, there was no observable change in FEV_1 (table 2). Secondarily, there was a significant reduction in the number of inpatient days; median −4 (IQR −17 to 0) days, and a significant reduction in the number of antibiotic treatment days for respiratory exacerbations, −21 (IQR −42 to 0) days. The magnitude of these effects was reduced for homozygous patients (table 3).

DISCUSSION

This retrospective observational longitudinal medicine use evaluation demonstrates that routine tezacaftor-ivacaftor use was associated with significant improvements in patients' weight, but not lung function. Tezacaftor-ivacaftor was also associated with a significant reduction in number of days spent in hospital and number of days receiving antibiotic treatment for cystic fibrosis–related respiratory exacerbations.

To the authors' knowledge, this is the first observational longitudinal cohort study to evaluate the efficacy and impact of tezacaftor-ivacaftor in routine clinical practice for adults with cystic fibrosis, rather than in a randomised controlled trial setting. While some may consider this study's small sample size to be a limitation, due to the potential for the study to be underpowered with a risk of type 2 statistical error, the study population was slightly larger than the numbers required to detect significant differences in a previous randomised controlled study (n=34) for differences in FEV_1.[14] Another strength of this study was that it was able to assess other measures which were not included in previous randomised controlled studies,[2 14] such as the number of days patients spent in hospital as inpatients, and the number of days that patients required antibiotics for respiratory exacerbations, all of which significantly impact on patients' personal lives and experiences. While we would have liked to have explored patients lived experiences before and after receiving tezacaftor-ivacaftor by evaluating quality of life, this was outwith the scope of this study due to the retrospective nature of the study.

Another strength of this study was that all patients received treatment within and from the West of Scotland Adult Cystic Fibrosis Unit for their courses of antibiotic treatment, inpatient

Table 2 Observed difference, 52 weeks before and after tezacaftor-ivacaftor (n=45)

Measure	Pre median (range)	Post median (range)	Median difference (IQR)	Wilcoxon ranked
FEV_1 (%)*	46.0 (17 to 83)	47 (18 to 112)	0 (–3 to 6)	Z=–1.133, p=0.257
Days in hospital	13 (0 to 81)	2 (0 to 91)	–4 (–17 to 0)	Z=–3.998, p<0.001
Days receiving antibiotics	56 (0 to 144)	28 (0 to 119)	–21 (–42 to 0)	Z=–4.159, p<0.001
	Mean (SD)	**Mean (SD)**	**Mean difference (95% CI)**	**Paired t-test**
Weight (kg)	62.3 (10.7)	64.0 (11.0)	1.8 (0.7 to 2.8)	p=0.002
BMI (kg/m^2)	21.8 (2.8)	22.5 (2.9)	0.6 (0.2 to 1.0)	p=0.003
Number of medicines	12.4 (4.7)	13.0 (5.0)	0.6 (-0.1 to 1.1)	p=0.045

*n=43, as two patients had not had respiratory function measured since starting tezacaftor-ivacaftor.
BMI, body mass index; FEV_1, forced expiratory volume in one second.

Table 3 Observed difference, 52 weeks before and after tezacaftor-ivacaftor, homozygous genotype (n=34)

Measure	Pre median (range)	Post median (range)	Median difference (IQR)	Wilcoxon ranked
FEV_1 (%)*	45.0 (17 to 83)	47 (18 to 85)	0 (–4 to 5)	Z=–0.043, p=0.965
Days in hospital	14 (0 to 81)	3 (0 to 91)	–4 (–18 to 0)	Z=–3.112, p=0.002
Days receiving antibiotics	56 (0 to 144)	38 (0 to 119)	–14 (–30 to 1)	Z=–3.074, p=0.002
	Mean (SD)	**Mean (SD)**	**Mean difference (95% CI)**	**Paired t-test**
Weight (kg)	60.7 (10.6)	62.3 (11.0)	1.5 (0.3 to 2.8)	p=0.016
BMI (kg/m^2)	21.3 (2.7)	21.8 (2.6)	0.5 (0.1 to 1.0)	p=0.024
Number of medicines	13.3 (4.5)	13.9 (4.8)	0.6 (-0.1 to 1.3)	p=0.092

*n=32, as two patients had not had respiratory function measured since starting tezacaftor-ivacaftor.
BMI, body mass index; FEV_1, forced expiratory volume in one second .

admissions and tezacaftor-ivacaftor treatment. This meant that all patients were treated according to the same standards of care, minimising variation in care received. This is in contrast with previous multicentre international studies where there can be national and regional variations in practice, as well as funding restrictions to accessing treatment.[2 14 21]

As with other studies, this study is not without its limitations. Unfortunately, due to the small sample size and a minority of patients being heterozygous, it was not possible to explore and assess differences in response for homozygote and heterozygote patients. Although the financial consequences of the changes in demand and practice due to fewer patients requiring hospital admission and antibiotics courses is of interest, these were outwith the scope of this study, but would be of value in considering future service developments. Concordance and patients' ability to comply with treatment may potentially affect this study's findings; however, while we cannot guarantee patients were fully compliant with treatment, it was known that patients did order their tezacaftor-ivacaftor regularly during the study period. Finally, although some may question the generalisability of this study, as it was conducted in one adult cystic fibrosis unit in Scotland, the findings may be of interest to others working in a similar setting within the UK and internationally.

Unfortunately, this study's finding that there was no significant difference in FEV_1 before and after tezacaftor-ivacaftor initiation was disappointing. These results were unlike the EVOLVE and EXPAND randomised controlled trials that evaluated tezacaftor-ivacaftor efficacy for patients with homozygous and heterozygous cystic fibrosis, demonstrating a 4.0% (95% CI 3.1% to 4.8%) and 6.8% (95% CI 5.7% to 7.8%) improvement in FEV_1, respectively.[2 14] The mean BMI of 22 kg/m^2 of patients in this study was comparable to 21 kg/m^2 of the EVOLVE study but lower than 24 kg/m^2 in the EXPAND study, with the median age of patients in this study being 30 years old compared with EVOLVE and EXPAND with mean ages of 27 and 36 years, respectively, on initiation of treatment. Unlike the EVOLVE study, where marginal improvements in BMI were observed,[2] this cohort of patients demonstrated a small statistically significant improvement in BMI. While longer-term follow-up is required to determine if BMI plateaus or continues to rise following initiation of tezacaftor-ivacaftor, this finding may help specialist dieticians tailor the nutritional advice that they give to patients receiving CFTR modulators. Finally, while we have compared our findings to EVOLVE and EXPAND, the longer duration of treatment in this study may confound comparisons, as it is known that people with cystic fibrosis lose 1%–3% of their lung function each year,[22] as well as the frequency of pulmonary function testing being less in routine practice. Patients in this cohort also had lower FEV_1 at baseline: median of 46% vs 60% and 62% in EVOLVE and EXPAND,[2 14] which may explain why we did not find a significant difference in FEV_1 following treatment with tezacaftor-ivacaftor as patients were less well at the point of initiation.

The number one challenge for service providers is providing equity of access for appropriate patients to tezacaftor-ivacaftor within limited budgets, within the UK and elsewhere, as CFTR modulators are and remain expensive. While these products have helped achieved significant improvements in some clinical measures, their cost-effectiveness has yet to be demonstrated, with data from the manufacturer's 5-year review in Scotland not expected until 2024. Yet as outlined above, there have been a number of initiatives in Scotland which have tried to enable tezacaftor-ivacaftor access and use for appropriate patients.

Another challenge for service providers is how the greater future use of CFTR modulators could influence the delivery of inpatient and outpatient care. Especially as starting and delivering antibiotic treatment is resource intensive and requires the expertise of several healthcare professionals across the multidisciplinary team, therefore reducing the number of courses of antibiotics that patients require will free capacity and healthcare professional's skills for other aspects of patient care. In terms of patient benefit, a reduction in frequency of antibiotic use will reduce the risk of patients developing antibiotic hypersensitivity reactions and/or bacterial resistance,[23] which also aligns with national objectives for antimicrobial stewardship.[24] It is also known that patients who experience more severe respiratory exacerbations have been shown to have a poorer health-related

What this paper adds

What is already known on this subject

⇒ Cystic fibrosis is a genetic condition characterised by a progressive decline in lung function, respiratory infections and early death.

⇒ Tezacaftor-ivacaftor has been shown to significantly improve lung function and reduce respiratory exacerbation rate in patients with cystic fibrosis in randomised controlled clinical trials.

⇒ A medicine use evaluation was warranted to assess the impact of prescribing tezacaftor-ivacaftor in the routine clinical care of adults with cystic fibrosis.

What this study adds

⇒ This study shows that tezacaftor-ivacaftor significantly improves body mass index (BMI), reduces days spent in hospital and reduces days spent receiving treatment with antibiotics, when prescribed to adults with cystic fibrosis in routine clinical care.

⇒ This study also shows that tezacaftor-ivacaftor was associated with small improvements in lung function which were unfortunately not statistically significant.

quality of life, therefore reducing exacerbation rate and hospitalisation is expected to improve quality of life.[25] But of more practical importance to patients and their families and carers is the fact that tezacaftor-ivacaftor use was associated with fewer hospital admissions and days in hospital, therefore reducing long journeys from remote and rural areas to Glasgow for treatment.

Unfortunately, an economic evaluation and cost consequence analysis was outwith the scope of this medicine use evaluation; however, it is important to note that a significant reduction in days spent in hospital as well as a reduction in antibiotic use will have important personal benefits for our patients and health service resources used to support people with cystic fibrosis, therefore future service evaluation studies may consider evaluating this in more detail. In relation to tezacaftor-ivacaftor use in routine practice, future studies should consider qualitative and quantitative studies to evaluate the impact of tezacaftor-ivacaftor on the quality of life of people with cystic fibrosis and their families and carers; assess the long-term outcomes and safety associated with its use; and assess if there are outcome differences between heterozygotes and homozygotes in relation to its use within routine practice.

In conclusion, the use of tezacaftor-ivacaftor in routine practice for people with cystic fibrosis was associated with small improvements in lung function which were unfortunately not statistically significant. There was however a significant improvement in BMI, and number of days spent in hospital and receiving antibiotics were also reduced. Further work is needed to evaluate the cost-effectiveness of tezacaftor-ivacaftor and to assess the impact of this medicine on the quality of life of people with cystic fibrosis.

Acknowledgements With thanks to Daniella Cornacchia, Pre-registration pharmacist, Queen Elizabeth University Hospital, Glasgow, for assisting with data collection; and Pauline McGuire, Principal Pharmacist, NHS Health Improvement Scotland, for reviewing this manuscript.

Contributors IP and CJ contributed to the conception and design of the work and the acquisition, analysis and interpretation of data. GM contributed to the conception of the work and analysis and interpretation of data. IP and CJ contributed to drafting the work and revising it critically for important intellectual content; final approval of the version published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GM contributed to revising the work critically for important intellectual content; final approval of the version published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests IP has received payment as an external speaker at a Vertex sponsored scientific event. CJ has no competing interests. GM has been the principal and chief investigator on a variety of Vertex studies, and has received funding from Vertex for investigator-led trials, attended advisory boards and received unrestricted educational grants on behalf of the Scottish Cystic Fibrosis Group.

Patient consent for publication Not required.

Ethics approval Ethical opinion was sought from the West of Scotland Research Ethics Service on the use of anonymised patient-level data for the study. The study was considered to be service evaluation and therefore did not require research ethics approval; however, Caldicott Guardian approval was sought and granted by NHS Greater Glasgow and Clyde (NHSGGC) Caldicott Guardian.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Individual participant data that underlie the results reported in this article, after deidentification, will be made available, beginning 3 months and ending 5 years after article publication. Data will be shared with researchers providing a methodologically sound proposal in order to achieve the aims in the approved proposal. Proposals should be directed to iona.paterson@ggc.scot.nhs.uk.

ORCID iD

Iona Paterson http://orcid.org/0000-0001-6341-9675

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