Medication adherence to CFTR modulators in patients with cystic fibrosis: a systematic review

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Shareable abstract (@ERSpublications)
Adherence to CFTR modulators ranged from 62% to 100%. This broad range may be caused by the different measurement strategies and more specifically by the different CFTR modulators. Larger studies with ETI and with standardised measurements are needed. https://bit.ly/4cjQ25y

Cite this article as: Hansen CME, Breukelman AJ, van den Bemt PMLA, *et al*. Medication adherence to CFTR modulators in patients with cystic fibrosis: a systematic review. *Eur Respir Rev* 2024; 33: 240060 [DOI: 10.1183/16000617.0060-2024].

Received: 20 March 2024
Accepted: 18 June 2024

Abstract

Background In the last decade, a fundamental shift in the treatment of cystic fibrosis (CF) took place due to the introduction of CF transmembrane conductance regulator (CFTR) modulators. Adequate medication adherence is a prerequisite for their effectiveness, but little is known about adherence to CFTR modulators. We aimed to assess the extent of medication adherence to CFTR modulators in patients with CF and assess which characteristics are associated with adherence.

Methods A systematic review following PRISMA guidelines was performed. Studies needed to report adherence to CFTR modulators. Main outcomes were: 1) level of medication adherence and 2) associations of demographic and/or clinical characteristics with adherence.

Results In total, 4082 articles were screened and 21 full-text papers were assessed for eligibility. Ultimately, seven studies were included. Most studies were retrospective and focused on adherence to ivacaftor or lumacaftor–ivacaftor with only one focusing on elexacaftor–tezacaftor–ivacaftor. The majority used pharmacy refill data with adherence determined with the proportion of days covered (PDC) or the medication possession ratio (MPR). One study additionally used electronic monitoring and patient self-reported adherence. Adherence was 0.62–0.99 based on pharmacy data (PDC or MPR), 61% *via* electronic monitoring and 100% *via* self-report. Age <18 years appeared to be associated with good adherence, as was a higher lung function.

Conclusions Despite the wide variety of adherence methods used, adherence to CFTR modulators is suboptimal, based on objective measures such as pharmacy refill data or electronic monitoring. CFTR modulator adherence measurement and definitions requires more standardisation with a preference for objective and granular methods.

Introduction

Cystic fibrosis (CF) is an autosomal recessive genetic disease, most commonly seen in the Caucasian population. Globally, the population size of people with CF is estimated to range from 70 000 to 90 000 [1]. While CF is associated with early mortality, life expectancy is increasing progressively due to newborn screening and new treatments [2].

Until 2012, airway clearance therapies, pancreatic enzyme replacement and antibiotics were mostly used to release mucus from the airways, help digest food and treat infections. Novel CF therapies target the

underlying CF transmembrane conductance regulator (CFTR) dysfunction, the CFTR modulators [3]. Since 2012, four different CFTR modulators have become available: ivacaftor, lumacaftor–ivacaftor, ivacaftor–tezacaftor and elexacaftor–tezacaftor–ivacaftor (ETI). These modulators initiated a fundamental shift in CF treatment [4]. Contrary to some previous CF treatments, CFTR modulators are taken orally, with potentially improved adherence compared to inhalation medication.

Medication adherence is the "process by which patients take their medications as prescribed" [5]. Non-adherence is a complex and multifactorial healthcare problem with causes that may relate to the patient, treatment and/or healthcare provider and system [6, 7].

Notably, management of CF includes a combination of different pharmacological treatment regimens, which can be a burden to patients. Still, adequate medication adherence is necessary for these regimens to work. Non-adherence has been associated with more hospitalisations and increased length of hospital stay in patients with CF. The consequences on the personal level can be large, resulting in worse health, not being able to work or enjoy family life, the need for transplantation and shortened life expectancy [8]. Additionally, non-adherence may lead to medication waste, with both environmental and economic consequences [9].

Adherence to CF treatments overall has been shown to range from 35% to 75% [6, 10, 11]. However, the majority of studies were published prior to the development of the CFTR modulators and therefore focused mostly on nebulisers and other symptomatic therapies [12]. Limited data are available on the extent of adherence to CFTR modulators. Because of the high effectiveness of the new CFTR modulators, a higher adherence may be expected. The fact that CFTR modulators are an oral therapy can also enhance adherence. Adherence to inhaled therapy (46%) was noticeably lower than adherence to oral therapy (74%) in patients with asthma [13]. This difference in adherence based on mode of administration can be explained by the fact that taking oral medication is technically less difficult and less time-consuming than taking inhalation medication. On the other hand, inhaled pulmonary therapy generally has less side-effects and can immediately relieve symptoms, making it potentially more attractive for some patients. Last but not least, higher adherence may be caused by the perception of scarcity of different types of medication.

The high effectiveness may, however, lead to non-adherence due to the lack of symptoms. A broad understanding regarding the extent, determinants and impact of medication non-adherence to CFTR modulators is currently lacking.

Therefore, the aim of this systematic review was to investigate current literature on medication adherence to CFTR modulators in patients with CF, with the extent of medication adherence and associations of demographic and clinical characteristics with adherence as main outcomes.

Methods

Study design

This systematic review was registered at PROSPERO (CRD42023400536) and was reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement (supplementary material S1) [14].

Information sources

A comprehensive search was conducted in the PubMed and Embase bibliographic databases for articles published between database inception and 18 December 2023.

Search strategy

The following search terms were used (synonyms and related words included) as controlled terms or free-text words: "cystic fibrosis" AND ("children" OR "patients" OR "adults" OR "young adults") AND "compliance". The full search strategy and synonyms used for both databases can be found in supplementary material S2. Of note, the search term "CFTR modulators' was not explicitly used in the search strategy because not all potentially relevant articles were found when piloting the search strategy with this term.

Eligibility criteria

Studies were eligible if the following inclusion criteria were met: 1) the study design was an intervention study (randomised controlled trial (RCT), non-RCT or before–after study) or an observational study (cohort, cross-sectional or case–control study) and 2) the study was published in English or Dutch. Reviews, systematic reviews, editorials, case reports and studies in a language other than Dutch or English

were excluded. References of reviews and backward citation searching were used to identify other potentially eligible studies. Due to the lack of detailed data, conference abstracts were not included in the main analysis of this review, but the data are briefly reported in the Results section and in the supplementary material.

Selection process

Titles and abstracts were independently screened by two reviewers. Any conflicts were resolved by discussion until consensus was reached. Subsequently, full-text papers were assessed for eligibility. Rayyan, a web application for systematic reviews, was used for all screening steps [15].

Data collection process and data items

Per article, data were independently extracted by two reviewers. Any differences were discussed and resolved until consensus was reached. Data items included: first author, country, publication year, study design, study population, type of medication, adherence definition, method of adherence measurement, timing of measurement, adherence outcome and factors associated with adherence.

Study outcomes

Main outcomes of interest were: 1) the extent of medication adherence to CFTR modulators and 2) associations of demographic and clinical characteristics with adherence.

Risk of bias assessment

The bias assessment for cohort and cross-sectional studies was carried out using the Newcastle–Ottawa Scale, which is based on three domains: 1) selection of study groups (maximum of 4 points), 2) comparability of groups (maximum of 2 points) and 3) ascertainment of exposure/outcome (maximum of 3 points). Studies with 6 points were classified as good quality, 4–5 points as moderate quality and ⩽3 points as low quality [16].

Results

Study selection

The database searches resulted in the identification of 4082 potentially eligible articles. Searching references of reviews provided two additional relevant studies. Elimination of duplicates yielded a total of 3186 unique studies. After screening of titles and abstracts, 21 potentially eligible studies remained. Full-text articles were obtained and assessed for eligibility. Finally, seven studies met the inclusion criteria and were included in this systematic review (figure 1). No studies were added after inspecting the references of these articles. Additionally, nine conference abstracts were identified.

Study characteristics

The main characteristics of the seven included studies are shown in table 1 [4, 8, 17–21]. Five studies were retrospective. Population sizes ranged from 16 to 2548 patients, with mean age varying between 20 and 29 years, with an age range between 6 and 70 years [4, 8, 17–19].

In four studies, the majority of the patients were adults. In three studies, patients were treated with ivacaftor, in two studies with lumacaftor–ivacaftor, in one study patients treated with three different modulators were included (ivacaftor, lumacaftor–ivacaftor and tezacaftor–ivacaftor) and in one study all available modulators were included (ivacaftor, lumacaftor–ivacaftor and tezacaftor–ivacaftor and ETI). Five studies were conducted in the USA [4, 8, 17, 20, 21], one in the UK [18] and the remaining one in France [17]. Bias assessment indicated that five studies were of good quality; the other studies were considered as moderate quality studies (supplementary material S3) [4, 8, 17–21].

A total of nine conference abstracts were found (supplementary material S4) [22–30]. Population sizes ranged from 20 to 980 patients, with paediatric and adult patients, and only in the abstract of Cristiani *et al.* [22] was an age range given: 10–44 years. The studies were conducted in multiple countries (UK, Ireland, Italy, Spain, Australia and USA). In one study, patients were treated with lumacaftor–ivacaftor, in three with ivacaftor (one used ivacaftor *versus* placebo), in one with ETI and in the remaining studies, patients were treated with modulators matching their mutation.

Measurements and outcome measures

Measurements, outcome measures and definitions of medication adherence varied across studies. Most studies used pharmacy refill data to assess adherence.

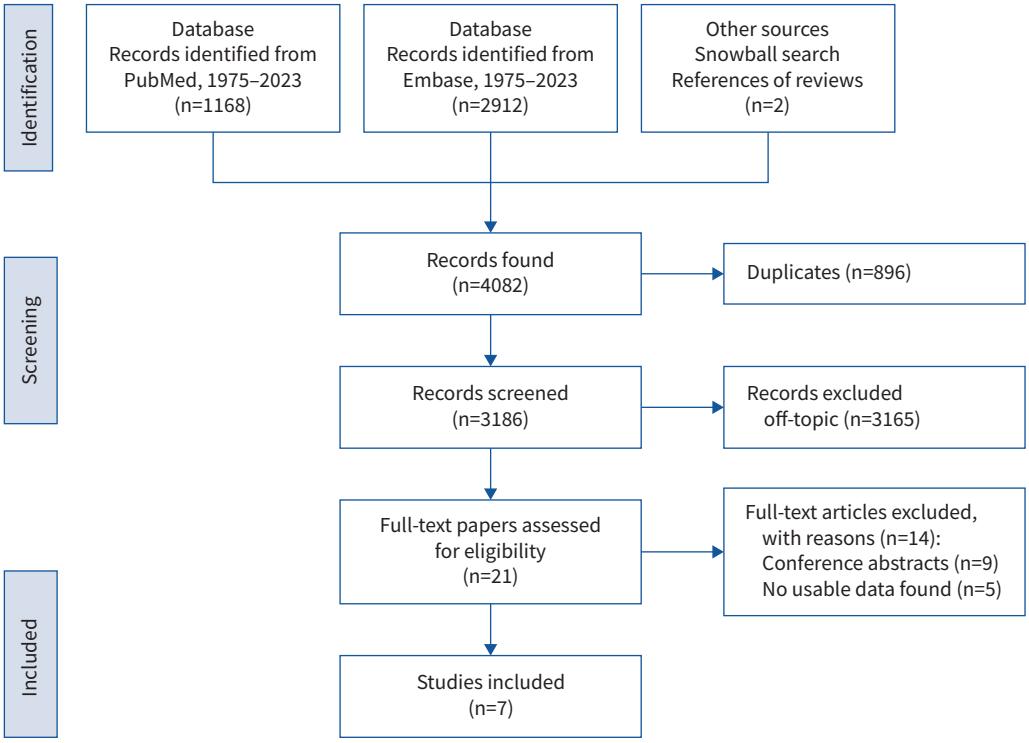

FIGURE 1 Study inclusion flowchart.

Olivereau *et al*. [17] calculated adherence using the proportion of days covered (PDC). PDC was calculated for 6 and 12 months after the date of treatment initiation, excluding days of hospitalisation. Good adherence to lumacaftor–ivacaftor was defined as PDC ⩾0.80, which was subsequently used to calculate the proportion of patients with good adherence.

Mehta *et al*. [20] utilised pharmacy refill data from a national specialty pharmacy to assess medication adherence to CFTR modulators. Adherence to three CFTR modulators (ivacaftor, lumacaftor–ivacaftor and tezacaftor–ivacaftor+ivacaftor) was calculated using PDC. PDC was calculated for patients that had more than one refill for the CFTR modulator they were using.

In the relatively small study (n=12) of Siracusa *et al*. [4], adherence to the CFTR modulator ivacaftor was analysed with the help of an electronic monitoring device, complemented by patient self-report measures and pharmacy refill data. The data from the electronic monitoring device were used to calculate overall adherence rates, weekly adherence rates and mean duration between doses. Adherence rates were calculated using the medication possession ratio (MPR) and by using the Aardex Medication Event Monitoring System (MEMS). With the data from the MEMS, an overall adherence rate was defined as: (total doses taken)/(total days monitored×2 doses per day). No definition of what was considered good adherence to a CFTR modulator was provided.

Suthoff *et al*. [21] used data from the Truven Health MarketScan Commercial Claims and Encounters Database (MSCCD) (US-based). Ivacaftor adherence was calculated with MPR. Good adherence was defined as the proportion of patients with MPR ⩾0.80 and again this was used to calculate the proportion of patients with good adherence.

In the study of Tesell *et al*. [19], data from three different sources were used: an internally managed prior authorisation system, the pharmacy claims procession system and the Medicaid Management Information System. The CFTR modulator investigated in this study was lumacaftor–ivacaftor. Adherence was calculated using PDC. Patients were categorised as adherent if PDC ⩾0.80, but no proportion of adherent patients was calculated.

Mitchell *et al*. [18] used data from a homecare delivery company that contacts patients monthly to monitor medication stock levels. Based on stock levels, orders were refilled when further supply was needed.

https://doi.org/10.1183/16000617.0060-2024

TABLE 1 Main characteristics of included studies (n=7)

First author, country, year [ref.]	Study design	Study population	Medication	Adherence definition	Data source	Timing of measurement	Adherence outcome	Factors potentially associated with adherence	NOS score
Siracusa, USA, 2015 [4]	Prospective cohort	n=12; age: 20.8±9.9 (range 6–48) years; adult: 50%; male: 50%; best FEV_1: 100.7±18.2% pred	Iva	Not reported	Electronic monitoring (MEMS); self-report; pharmacy refill data	Prevalent users (⩾1 month use) with average monitoring follow-up period of 118±35 days	Mean adherence MEMS-derived: 0.61±0.28 MPR: 0.84±0.31 Self-report: 100% with one exception (at enrolment and 3–4 months later)		6
Platt, USA, 2023 [8]	Retrospective cohort	n=191; average age TCP group: 19.9 years; average age non-TCP group: 20.7 years; age range: 0–70 years; male TCP group: 44%; male non-TCP group: 43%	All CFTRm	PDC ⩾0.80	Pharmacy refill data from a health system specialty pharmacy	Prevalent users between January 2017 and December 2020	Mean PDC TCP group CFTRm# year 1 overall: 0.85±0.17 CFTRm# year 2 overall: 0.83±0.17 CFTRm# year 3 overall: 0.77±0.17 ETI year 1 overall: 0.91±0.13 ETI year 2 overall: 0.91±0.10 Non-TCP group CFTRm# year 1 overall: 0.77±0.22 CFTRm# year 2 overall: 0.80±0.18 CFTRm# year 3 overall: 0.74±0.25 ETI year 1 overall: 0.90±0.14 ETI year 2 overall: 0.86±0.16		7
Olivereau, France, 2020 [17]	Retrospective cohort	n=96; age: 22±9 (range 12–>35) years; adult: 55%; male: 54%; mean FEV_1: 77±25% pred	Lum–Iva	PDC ⩾0.80	Pharmacy refill data	First 6 and 12 months after treatment initiation	Mean PDC (capped at 1.00) 6 months: 0.93 12 months: 0.90 Adherent patients (PDC ⩾0.80) 6 months: 89% 12 months: 83%	Age (for each additional year): OR 1.13 (95% CI 1.004–1.28) FEV_1 % pred (for each additional 1%): OR 1.04 (95% CI 1.005–1.08) Sex, BMI, chronic *P. aeruginosa* infection and travel time to pharmacy not significant	8
Mitchell, UK, 2021 [18]	Retrospective cohort	n=35 (MPR available for n=33); age: 29.06±9.54 (range 14–34) years; male: 57%	Iva	Not reported	Refill data from homecare delivery company	2 years prior to index data (starting Iva) up to 5 years following initiation	Mean MPR 3 months: 0.99±0.03 60 months (n=26): 0.88±0.05 Median MPR 3 months: 1.0 (1.0–1.0) 60 months (n=26): 1.0 (0.78–1.0)	FEV_1: p=0.036 (overall MPR–FEV_1 change from baseline at 60 months) FEV_1: p=0.006 (annual MPR–FEV_1 change from previous year) BMI: p=0.027 (overall MPR–BMI); no relationship between overall MPR and BMI change from baseline at 60 months or annual MPR with BMI change from previous years	7

Continued

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TABLE 1 Continued

First author, country, year [ref.]	Study design	Study population	Medication	Adherence definition	Data source	Timing of measurement	Adherence outcome	Factors potentially associated with adherence	NOS score
Tesell, USA, 2019 [19]	Pre–post	n=21; age: 20.1 (range 12–51) years; majority of patients: male[¶]	Lum–Iva	PDC ⩾0.80	Pharmacy claims processing system, internally managed PA system and MMIS	6 months after index date (first pharmacy claim)	Mean PDC: 0.62±0.29 Minority of patients were adherent (PDC ⩾0.80)[¶]		5
Mehta, USA, 2021 [20]	Retrospective cohort	n=2548; age: 23.0±13.7 years; adult: 57.8%; male: 54.4%; mean FEV_1 % pred: not available	Iva (30.8%); Lum–Iva (50.6%); Tez–Iva+Iva (18.6%)	Not reported	Pharmacy fill data from national specialty pharmacy	Prevalent users between September 2017 and August 2018	Mean PDC Total: 0.86±0.15 Iva: 0.84±0.16 Lum–Iva: 0.84±0.15 Tez–Iva+Iva: 0.92±0.11	PDC according to age Children/adolescents (<18 years) Total: 0.86±0.14 Iva: 0.85±0.15 Lum–Iva: 0.86±0.14 Tez–Iva+Iva: 0.96±0.10 Adults (⩾18 years); p-values t-test (*versus* children/adolescents) Total: 0.85±0.15; p=0.0876 Iva: 0.84±0.16; p=0.3744 Lum–Iva: 0.83±0.15; p=0.0001 Tez–Iva+Iva: 0.91±0.11; p=0.001	6
Suthoff, USA, 2016 [21]	Retrospective cohort	n=79; age: 20.8±11.8 years; male: 46%	Iva	MPR ⩾0.80	MSCCD database	Prevalent users between 1 January 2012 and 31 July 2014	Mean MPR Total: 0.80±0.3 Single-month supply: 0.80±0.3 Multi-month supply: 0.90±0.2 Adherent patients (MPR ⩾0.80): 73.4%		5

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. NOS: Newcastle–Ottawa Scale; FEV_1: forced expiratory volume in 1 s; Iva: ivacaftor; MEMS: Medication Event Monitoring System; MPR: medication possession ratio; TCP: total care pharmacy; CFTRm: cystic fibrosis transmembrane conductance regulator modulators; Lum: lumacaftor; ETI: elexacaftor–tezacaftor–ivacaftor; PDC: proportion of days covered; BMI: body mass index; *P. aeruginosa*: *Pseudomonas aeruginosa*; PA: prior authorisation; MMIS: Medicaid Management Information System; Tez: tezacaftor; MSCCD: MarketScan Commercial Claims and Encounters. [#]: excluding ETI; [¶]: exact percentage not reported.

The CFTR modulator investigated in this study was ivacaftor. To calculate adherence rates, the MPR was calculated quarterly, yearly and overall. No definition of what was considered good adherence was provided.

Finally, Platt *et al.* [8] used refill data from a specialty pharmacy. Patients were grouped by age and whether or not they were enrolled in a service called total care pharmacy (TCP). Adherence was calculated by using the PDC, and the primary outcome was the difference in mean PDC between the TCP and non-TCP groups.

Extent of medication adherence to CFTR modulators

Mean PDC/MPR, based on pharmacy refill data or the MSCCD database (US-based), ranged from 0.62 to 1.0 (figures 2 and 3) [4, 8, 17–21]. Two studies also reported the proportion of adherent patients: 73% and 89%, respectively [17, 21]. Adherence based on electronic monitoring and self-report was 0.61 and 1.0, respectively [4].

Studies in which patients were treated with ivacaftor reported mean MPRs of 0.80, 0.84, 0.84 and 0.99 at 3 months and 0.87 at 60 months [4, 18, 20, 21]. Mean PDCs in patients who used lumacaftor–ivacaftor were 0.93, 0.84 and 0.62 [17, 19, 20]. A mean PDC of 0.92 was found in patients treated with tezacaftor–ivacaftor (figure 2) [20]. In the group of patients treated with ETI, an overall PDC of 0.91 was found in both year 1 and 2. In the non-TCP group, overall PDCs were 0.89 and 0.86 in year 1 and 2, respectively [8]. Time-dependent variation was observed depending on whether starters or prevalent users of CFTR modulators were included and length of follow-up. Generally, the longer after start, the lower the adherence [4, 8, 17–21].

Mitchell *et al.* [18] showed that the mean MPR was 0.99 after 3 months and 0.88 after 60 months. The rate of decline was 0.025 per year.

Factors associated with medication adherence to CFTR modulators

Several studies assessed factors associated with medication adherence to CFTR modulators [17, 20]. Two articles described an association between age and medication adherence [17, 20]. For their study population (mean±SD age 22±9 years), Olivereau *et al.* [17] showed an OR for each additional year of age of 1.13 (95% CI 1.004–1.28), suggesting a higher adherence in older patients. The age distribution between adherent and non-adherent patients was unequal.

Mehta *et al.* [20] reported that children/adolescents (<18 years) that were treated with lumacaftor–ivacaftor and tezacaftor–ivacaftor+ivacaftor had a statistically significantly higher mean PDC (0.86 and 0.96, respectively) than adults (0.83 and 0.91, respectively), suggesting a higher adherence in younger patients [20].

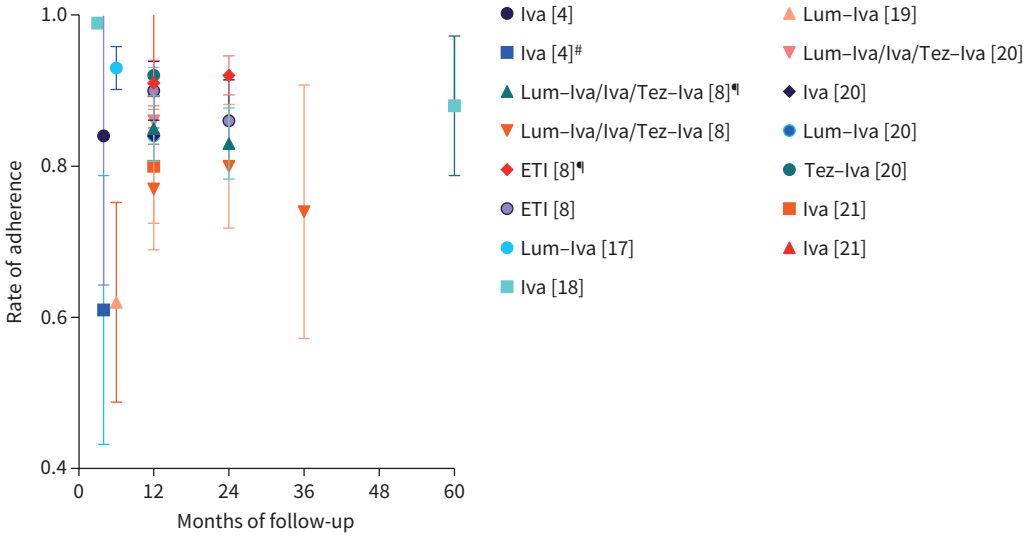

FIGURE 2 Adherence rates to cystic fibrosis transmembrane conductance regulator modulators. Rates are given as mean±SD medication possession ratio or proportion of days covered. #: electronic monitoring; ¶: intervention group. Iva: ivacaftor; Lum: lumacaftor; Tez: tezacaftor; ETI: elexacaftor–tezacaftor–ivacaftor.

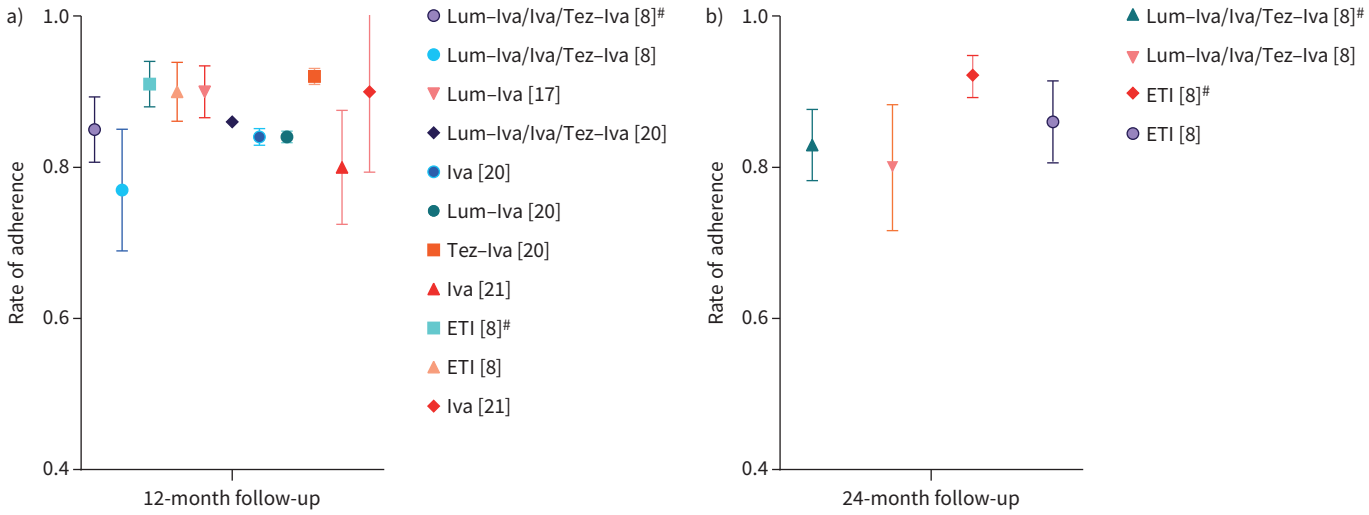

FIGURE 3 Adherence rates to cystic fibrosis transmembrane conductance regulator modulators: detailed overview of the a) 12- and b) 24-month follow-ups as shown in figure 2. Rates are given as mean±SD medication possession ratio or proportion of days covered. #: intervention group. Iva: ivacaftor; Lum: lumacaftor; Tez: tezacaftor; ETI: elexacaftor–tezacaftor–ivacaftor.

Besides age, percentage predicted forced expiratory volume in 1 s (FEV_1) was found to be statistically significantly associated with adherence in the study of Olivereau *et al.* [17].

The study of Mitchell *et al.* [18] showed that patients with a higher overall MPR had a greater FEV_1 change from baseline at 60 months (p=0.036). Furthermore, they showed an association between a higher annual MPR with a reduced rate of decline in FEV_1 from the previous year (p=0.006). Finally, they found a significant negative association between overall MPR and body mass index (BMI). However, no associations between overall MPR and BMI change from baseline at 60 months or annual MPR with BMI change from the previous year were found.

Conference abstracts

All but one of the nine identified abstracts used pharmacy data to measure adherence to CFTR modulators. Three studies additionally used patient self-report questionnaires [22–24]. Mean PDC/MPR, based on pharmacy data and MarketScan commercial claims, ranged from 0.39 to 0.99 [22–30]. Adherence based on self-report ranged from 50% to 99% [22–24]. Of note, according to Sutton *et al.* [23], the one abstract that used electronic monitoring, self-report and refill data overestimated the adherence compared to electronic monitoring. Two studies indicated that patients who received their medication at a specialty pharmacy had a higher adherence than patients who did not [22, 26].

Discussion

Main findings

This systematic review revealed that there is a paucity of data regarding the extent of adherence to CFTR modulators among patients with CF. The available data, based on heterogenous definitions and measurements of adherence, indicated that adherence is suboptimal. Two studies indicated an association of age with adherence and one study showed that a higher percentage predicted FEV_1 was associated with better adherence.

Furthermore, for most CFTR modulators, the longer the follow-up, the lower the adherence. No difference in adherence was found between the different modulators.

Interpretation

While we found that adherence to CFTR modulators is suboptimal, adherence to inhaled therapies used in CF, such as dornase alfa, tobramycin and hypertonic saline, is even lower, ranging from a composite MPR of 0.4 to an all daily adherence value of 0.57 [12, 31]. Although underlying populations, methods of measurement and definitions of adherence varied, our finding of higher adherence for the oral CFTR modulators is in line with a study by Price *et al.* [13] that directly compared the two methods of

administration, revealing that adherence to inhaled therapy (46%) was noticeably lower than adherence to oral therapy (74%) in patients with asthma. Given the high variation in effectiveness of different CFTR modulators for different kinds of mutations, a between-drug difference in adherence may be expected. For example, the efficacy of the CFTR modulators lumacaftor–ivacaftor and tezacaftor–ivacaftor compared to the highly effective modulator therapies of ivacaftor (for gating mutations) and ETI is very different. A difference in adherence between these CFTR modulators may be expected. The studies included in this review did not report such a difference [4, 8, 17–21].

However, the one study addressing adherence to ETI, a highly effective modulator in many CF patients, showed an extremely high mean and median PDC for ETI in the 2 years of follow-up compared to the other CF medication (dornase alfa, inhaled hypertonic saline and CFTR modulators excluding ETI). There might be an association between higher adherence to the highly effective modulators and higher tolerability rates and efficacy. On the other hand, high effectiveness may lead to non-adherence due to lack of experienced symptoms. However, a longer follow-up study is needed as the follow-up for ETI was only 2 years while most notable reductions on adherence to other CF medications were between year 2 and 3.

Most studies included in this review solely used pharmacy refill data for adherence measurement. While these data can be easily obtained, it is not the most reliable method. Using pharmacy data, there is no insight into day-to-day variation in intake, the actual intake of the medication or the number of prescribed medications patients still have at home [32]. More direct and granular measurements of intake, such as electronic monitoring, may therefore be preferred.

Additionally, limited information was available about the patients' clinical characteristics and their day-to-day adherence behaviour. More information about clinical aspects would be helpful to gain more insight into specific patient-level predictors for non-adherence and its clinical consequences. As illustrated by Siracusa *et al*. [4], self-report overestimates adherence when compared to pharmacy data and electronic monitoring, a finding that was confirmed in the study by Sutton *et al.* [23].

The different methods for measuring adherence each have advantages and disadvantages. Self-reported questionnaires are easy to use and inexpensive, but can overestimate adherence, are subjective and influenced by recall or reporting bias. In self-reported questionnaires, a relatively poor sensitivity and specificity can occur due to false data input by patients, purposefully or accidently. Also, poor communication skills and questions constructed by the interviewers as well as the design of the survey can introduce bias in this method of data collection. Furthermore, when questions are negatively described, suggesting that the patient is to blame for not fulfilling the prescribed regime, this may also lead to bias. Last but not least, the psychological state of a patient can impact the response on a self-reported questionnaire [33].

Therefore, it is advised to combine self-report questionnaires with more objective measurements. Furthermore, when non-adherence is detected, a patient should be asked about the reasons for non-adherence. Electronic databases (allowing calculation of MPR or PDC), on the other hand, are also easy to use, inexpensive, non-invasive and specific to identify non-adherent patients. Yet, data are non-granular (with dispenses typically varying between 1 and 3 monthly) and there is no evidence that the medication is actually ingested.

It is important to highlight the difference between the MPR and the PDC calculation. MPR is defined as "the proportion of days supply obtained during a specified time period or over a period of refill intervals". PDC is the number of days when the drug was available divided by the number of days in the study period [34].

The MPR calculation is very simple, but one of the main disadvantages is that it does not consider the gaps in refills and therefore the need for continuous therapy with multiple prescriptions. With MPR, in comparison to PDC, an overestimated adherence rate can be found [33]. The difference between these two calculations can be a problem when interpreting results of the included studies, *i.e.* the differences in adherence may be partially due to the different measurement methodologies.

Electronic monitoring systems are objective and one of the most accurate methods, but the patient is aware of the evaluation and still there is no evidence that the medication is being ingested [34]. Notably, none of the aforementioned methods provides data on reasons for non-adherence. Finally, the cut-off to define a patient as non-adherent is a matter of debate. In the literature, a cut-off of 80% intake of the prescribed dose is often quoted, but the actual cut-off can vary between medicines and patients based on

pharmacokinetic properties and the relative forgiveness (*i.e.* clinical consequence) of missing a dose. For CFTR modulators, this should be a subject of future research. It may well be that adherence slightly wanes over time, but still remains acceptable and does not put the patient at risk of poor outcomes.

Two studies showed an association between age and adherence, with apparently conflicting results regarding adherence in higher age groups [17, 20]. We hypothesise that most children receive help and guidance from their parents regarding medication intake, supporting their adherence. Emerging into adulthood, patients undergo a variety of transitions such as going to college, starting a career and moving out. Due to the high treatment burden, all these changes may influence medication adherence [35]. Besides age, two studies found a positive association between higher percentage predicted FEV_1 and adherence [17, 18]. To establish a causal association, larger, longer term studies with less bias potential and more objective adherence measurements are needed.

In the studies in this review, only a limited number of factors were analysed regarding their association with adherence. From previous studies, we know that factors such as side-effects, unwillingness to take medication, financial barriers, holidays, weekends, summer or depression can also be associated with non-adherence [36]. Finally, the observed trend of lower adherence with longer follow-up emphasises the need for ongoing attention to the issue of adherence support over time.

Strengths and limitations

To the best of our knowledge, this is the first systematic review into the extent of adherence to CFTR modulators. Studies from two different databases were included and all studies were screened independently by two reviewers, increasing the reliability of this review. Results were structurally reported following PRISMA guidelines.

An obvious limitation of this review is the scarcity of studies on this particular topic. Abstracts were therefore included, but they provided only limited data (*e.g.* on population characteristics). Furthermore, in five out of the seven studies, study populations were small (less than 100 patients). Most of the studies were conducted in the USA, limiting generalisability to other countries. The heterogeneity in adherence measurement methods and definitions made it difficult to perform a meta-analysis and draw firm conclusions, although in general the studies show that there is room for adherence improvement.

Finally, only one of the studies identified reported adherence to the highly effective modulator therapy ETI. More high quality research is needed to gain insight into longer term adherence to the highly effective modulator ETI; such studies should use standardised measurement methods and definitions to evaluate adherence [8]. Of note, one of the studies that may provide more insight into adherence to ETI is the large RECOVER study. In the RECOVER study, adherence is measured using three methods: 1) self-reported using the Treatment Adherence Questionnaire and Adherence Barrier Questionnaires, 2) MPR calculated from pharmacy refill data, and 3) electronic monitoring by MEMS (used for a subset of participants) [37].

Implications for future research

Given that non-adherence can lead to CF complications and high healthcare costs, it is of importance to identify the possible barriers to CFTR modulator adherence. Future review studies should look into this subject. The information from such studies could help to design a tool that can assist in identifying the reasons for non-adherence and may consist of a CF-specific adherence questionnaire. For asthma and COPD, such a novel tool has already been developed, *i.e.* the Test of Adherence to Inhalers (TAI) Toolkit [38]. The TAI Toolkit is a toolkit that can be used to identify barriers for adherence and subsequently it guides the healthcare professional to an evidence-based individualised intervention that is linked to the actual reason for non-adherence. By designing a CF-specific adherence questionnaire, this may be also achieved. Given the limitations of self-reporting, such a questionnaire should be combined with other, preferably direct measurements, *e.g.* by using digital adherence measurement technologies or bioanalytical measures such as medication levels in blood [39–41]. Possibly other matrices such as hair could be used, but this requires further research into actual CFTR modulator exposure [42].

To this point, only a very limited number of studies used objective and reliable methods of adherence measurement, requiring larger and longer term studies using these methods.

Furthermore, when adherence can be objectively measured, the next step is to develop interventions to improve adherence, possibly also supported by digital adherence technologies [43]. To fulfil the needs of patients and healthcare professionals, interventions need to be tailored as much as possible.

In conclusion, adherence to CFTR modulators is suboptimal. Potential associations of age and percentage predicted FEV_1 with adherence were found, but need confirmation in larger studies. Enhanced CF medication adherence measurement strategies should be developed and standardised.

Questions for future research

- Given non-adherence can lead to CF complications and high healthcare costs, it is of importance to identify the possible causes of non-adherence. The high costs of the CFTR modulators are largely based on their effectiveness. Non-adherence will lead to reduced effectiveness and thus an increase in healthcare costs. Therefore, a novel tool needs to be developed to specifically and systematically inquire about reasons for poor adherence. This may be achieved by designing a CF-specific adherence questionnaire. Because of the limitations of self-reporting, such a questionnaire should be combined with other, preferably direct measurements, *e.g.* by using digital adherence measurement technologies or bioanalytical measures such as measurements in plasma/blood and medication concentrations in hair. The latter measurement is one that can already be used for determining tacrolimus levels, for example, and could be developed to determine CFTR modulator concentrations.
- Overall, larger and longer term studies using objective and reliable methods of adherence measurement are needed as well as larger studies to confirm potential associations between patient characteristics and adherence.
- Last but not least, larger studies are needed to gain more insight in the long-term adherence of CFTR modulators, specifically for the newest modulator ETI.

Provenance: Submitted article, peer reviewed.

Author contributions: C.M.E. Hansen and A.J. Breukelman: conceptualisation, methodology, investigation, writing (original draft). P.M.L.A. van den Bemt, L. van Dijk and J.F.M. van Boven: methodology, supervision, writing (review and editing). A.M. Zwitserloot: methodology, writing (review and editing).

Conflict of interest: C.M.E. Hansen received a travel grant for the ECFS in 2023 (money paid to institution). A.M. Zwitserloot reports grants from Vertex Pharmaceuticals (IIS-2018-107391) and participation in an advisory board meeting for Sanofi (money paid to institution). J.F.M. van Boven reports consulting and advisory grants from Vertex (money paid to institution). The other authors declare that they have no know competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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