DRUG INTERACTIONS

The pharmacokinetic interaction between ivacaftor and ritonavir in healthy volunteers

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AIMS

The aim of this study was to determine the pharmacokinetic interaction between ivacaftor and ritonavir.

METHODS

A liquid chromatography mass spectrometry (LC–MS) method was developed for the measurement of ivacaftor in plasma. An open-label, sequential, cross-over study was conducted with 12 healthy volunteers. Three pharmacokinetic profiles were assessed for each volunteer: ivacaftor 150 mg alone (study A), ivacaftor 150 mg plus ritonavir 50 mg daily (study B), and ivacaftor 150 mg plus ritonavir 50 mg daily after two weeks of ritonavir 50 mg daily (study C).

RESULTS

Addition of ritonavir 50 mg daily to ivacaftor 150 mg resulted in significant inhibition of the metabolism of ivacaftor. Area under the plasma concentration–time curve from time 0 to infinity ($AUC_{0-\infty \text{ obs}}$) increased significantly in both studies B and C compared to study A (GMR [95% CI] 19.71 [13.18–31.33] and 19.77 [14.0–27.93] respectively). Elimination half-life ($t_{1/2}$) was significantly longer in both studies B and C compared to study A (GMR [95% CI] 11.14 [8.72–13.62] and 9.72 [6.68–12.85] respectively). There was no significant difference in any of the pharmacokinetic parameters between study B and study C.

CONCLUSION

Ritonavir resulted in significant inhibition of the metabolism of ivacaftor. These data suggest that ritonavir may be used to inhibit the metabolism of ivacaftor in patients with cystic fibrosis (CF). Such an approach may increase the effectiveness of ivacaftor in 'poor responders' by maintaining higher plasma concentrations. It also has the potential to significantly reduce the cost of ivacaftor therapy.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Ivacaftor is metabolized by cytochrome P450 3A4 and as such is subject to pharmacokinetic interactions with drugs that affect this enzyme.
- Ketoconazole has been shown to interact with ivacaftor such that a dose reduction of ivacaftor from 150 mg twice daily to 150 mg twice weekly is necessary.
- There is currently no literature published on the interaction between ritonavir and ivacaftor in healthy volunteers.

WHAT THIS STUDY ADDS

- This study investigates the pharmacokinetic interaction between ritonavir 50 mg daily and ivacaftor 150 mg in healthy volunteers.
- Exposure to ivacaftor is significantly increased and half-life of ivacaftor is significantly prolonged in the presence of ritonavir.
- This pilot study will inform the design of future studies in patients on ivacaftor therapy to explore the possibility of using ritonavir to increase the dosing interval of ivacaftor in clinical practice, thereby significantly reducing the budget impact of this high-cost drug.

Tables of Links

TARGETS	
Other ion channels [2]	Enzymes [3]
CFTR	CYP3 family

LIGANDS	
Cobicistat	Ketoconazole
Ivacaftor	Ritonavir

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2, 3].

Introduction

In 2012 ivacaftor became the first disease-modifying agent available for the treatment of cystic fibrosis (CF), an inherited condition that may be caused by a number of distinct genetic mutations that lead to either qualitative or quantitative defects in the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride channel on the surface of the cells that secrete mucus and sweat [4]. It is the most common inherited disease in Ireland, where there are currently over 1100 patients with the condition [5]. A defect in the CFTR leads to the production of thick, viscous secretions that precipitate repeated infections in the respiratory tract, damage to the pancreas and poor absorption of nutrients, ultimately resulting in a much-shortened life span — the median age at death for patients with CF in Ireland was 26.9 years in 2014 [5]. Ivacaftor is a small molecule that binds to the CFTR with the G551D mutation and increases the open probability of the channel, thus partially normalizing the movement of ions and water across the cell membrane and decreasing the viscosity of secretions [6]. The G551D mutation is associated with a severe phenotype of CF and is present in approximately 11% of persons with CF in Ireland [5].

The results of the pivotal trial of ivacaftor in patients 12 years or older with the G551D mutation, the STRIVE study sponsored by Vertex Pharmaceuticals, reported a striking average 10.4% increase in the primary endpoint, percentage predicted forced expiratory volume in 1 s (ppFEV₁), at 24

weeks in the treatment group; a relative increase compared to standard treatment of 10.6%. This improvement was sustained throughout the total 48 weeks of the trial. Several other improvements were demonstrated with ivacaftor therapy such as increased weight, decreased pulmonary exacerbations and improved quality of life [6].

While ivacaftor was shown in this trial to result in significant improvements in many aspects of the CF disease process for a sizable proportion of patients, it is noteworthy that an improvement in ppFEV₁ of 5% or more (deemed to be clinically significant) was seen in only 75% of the treatment group in the trial. It was not clear from a subgroup analysis why 25% of patients did not have this improvement. The numbers in the subgroup analysis were small and thus the drivers behind this were unclear, but it was not reported if variability in drug levels contributed to the difference in clinical outcome [6]. There is currently no sufficiently precise pharmacodynamic/pharmacokinetic model in the literature to inform the ideal plasma level of ivacaftor that patients need to maintain [7]; however, in an analysis published by the Food and Drug Administration in 2015, a linear relationship was seen between plasma ivacaftor levels and improvement in ppFEV₁ up to the third quartile of plasma concentrations in the treatment group, indicating that many patients may be maintaining suboptimal drug levels during the dosing interval [8]. Drugs such as ivacaftor that are metabolized by the mixed function oxidase CYP3A4 usually demonstrate significant inter-individual variability due to both genetic variations in the enzyme and environmental factors such as undetected inhibition/induction, disease

states and age [9, 10]. This variability is seen in the standard deviations of the major pharmacokinetic parameters reported in the summary of product characteristics for ivacaftor: after oral administration of a single 150 mg dose to healthy volunteers in a fed state, the mean ($\pm$ SD) for area under the concentration–time curve (*AUC*) and maximum concentration (*C*_{max}) were 10 600 (5260) ng.h ml⁻¹ and 768 (233) ng ml⁻¹, respectively [11].

There is existing clinical evidence that use of CYP3A4 inhibitors can overcome this problem of interindividual variability in CYP3A4 metabolism, increasing plasma levels throughout the dosing interval and also allowing for reduced dosing of the original drug, in this case, ivacaftor. The use of CYP inhibitors is well established in the treatment human immunodeficiency virus (HIV) infection for instance, with ritonavir boosting of other protease inhibitors now established as standard of care [12, 13]. The use of ritonavir for pharmacokinetic enhancement in the early years of HIV treatment enabled patients to take far fewer tablets over the course of the day, and those that did not achieve viral suppression due to low plasma levels of protease inhibitor became virally suppressed with the addition of ritonavir with the subsequent increase in plasma levels of co-administered protease inhibitors. The addition of a small dose of ritonavir to the medication regime for HIV meant that treatment became more convenient and more clinically effective for a larger number of patients [14].

In addition to clinical effectiveness, the issue of cost effectiveness is extremely pertinent in the case of ivacaftor. The drug acquisition cost to treat one patient with ivacaftor is €234 804 per annum [15]. Ivacaftor is one of the most expensive drugs reimbursed in Ireland at present and, due to the nature of the drug and the disease it treats, lifelong treatment is essential.

Given these issues with the clinical and cost effectiveness of ivacaftor treatment, this study investigates the pharmacokinetic interaction between ivacaftor and ritonavir *in vivo* in healthy volunteers to establish whether a CYP inhibitor can be used to alter the metabolism of ivacaftor in such a way that will allow for a longer dosing interval of the drug while at the same time increasing plasma levels of the drug.

Subjects and methods

Subjects

Subjects eligible for inclusion in this trial were healthy volunteers over the age of 18, able to give informed consent and not on any regular medications. To be classified as 'healthy volunteers', subjects underwent medical history, physical examination and laboratory tests including full blood count, urea and electrolytes, liver function tests, HIV and hepatitis serology, urine drug screen and pregnancy testing for women of child-bearing age. If female and of child-bearing potential or if male with a partner of child-bearing potential, volunteers had to be willing to use effective contraception during the study and up to 18 days after the last study day. The use of hormonal contraception was not permitted. Subjects were excluded if, in the opinion of the investigator, they had any medical condition that would put the subject at risk by participation in the study or influence the study result. Regular use of cigarettes or any substance that may induce or inhibit the cytochrome P450 system also resulted in exclusion. Volunteers were advised to avoid both drinking grapefruit juice and eating cruciferous vegetables for 1 week before the study and throughout the duration of the study. Over-the-counter medications, caffeine and alcohol were avoided 24 hours before the study commenced and throughout the duration of the study.

Study design

This was a single-centre, open-label, sequential, cross-over study with 12 healthy volunteers. A balanced trial design was achieved by randomizing subjects into three sequences of three periods representing a Latin square (Figure 1).

Study A consisted of administration of ivacaftor alone and measurement of ivacaftor plasma levels at 0, 1, 2, 3, 4, 6, 8, 10 and 12 h. Study B consisted of administration of ivacaftor and ritonavir 50 mg at time 0 and further administration of ritonavir 50 mg at 24, 48 and 72 h. Ivacaftor levels were measured at 0, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72 and 84 h. To investigate any induction effect of ritonavir, study C consisted of administration of 50 mg of ritonavir daily for 2 weeks prior to administration of ivacaftor 150 mg and ritonavir 50 mg at each of days 0, 1, 2 and 3. Ivacaftor levels

Figure 1

Study schema. Study A: Ivacaftor 150 mg. Study B: Ivacaftor 150 mg plus ritonavir 50 mg on days 0, 1, 2 and 3. Study C: Ritonavir 50 mg daily $\times$ 2 weeks then ivacaftor 150 mg plus ritonavir 50 mg on days 0, 1, 2 and 3

were measured at 0, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72 and 84 h. Standardized, high-fat meals were given to all volunteers for the first 12 h of each study and water was freely available throughout. Ritonavir liquid was administered with a small amount of chocolate milk to improve palatability as required. It was written into the original trial protocol that should ritonavir 50 mg not result in significant inhibition of the metabolism of ivacaftor at interim analysis of data after the completion of studies A, B and C, studies A, B and C would then go on to be repeated in the same manner with ritonavir at a dose of 100 mg. The lower dose of ritonavir was investigated first as the overall aim of the study was to ascertain the lowest dose of ritonavir that would provide significant inhibition of ivacaftor metabolism, thus minimizing any potential adverse effects of long-term exposure to ritonavir, some of which have been shown to be dose related [16–18]. Potential induction effects of ritonavir were also predicted to be minimized by the use of the smallest dose feasible [19].

Blood samples were collected in 5 ml tubes containing ethylenediaminetetraacetic acid (EDTA). These were centrifuged for 10 min at room temperature immediately after collection and the plasma supernatant aliquoted into 300 μ l fractions and frozen at -80°C .

The main pharmacokinetic parameters assessed in the study included $t_{1/2}$ of ivacaftor in the absence and presence of ritonavir, change in C_{max} and time to maximum concentration (t_{max}) and the area under the time–concentration curve (AUC) of ivacaftor in the presence and absence of ritonavir. Variability in the above pharmacokinetic parameters was also assessed in the absence and presence of ritonavir.

Ethical approval for the study was obtained from the Tallaght Hospital/St James's Hospital Joint Research Ethics Committee on 11 May 2015 (reference number 2015/04/03/2015-05 list 19[1]). The clinical trial protocol was submitted to the Health Products Regulatory Authority and approval for the study was obtained on 1 May 2015.

LC–MS analysis

LC–MS analyses were performed on an Agilent 1100 high performance liquid chromatography (HPLC) system equipped with a G13795 degasser, G1312A BinPump, a G1313A ALS and G1316A column oven (COLCOM) (Agilent, Little Island, Cork). Separation was obtained on an Allure PFP Propyl column (5 μm , 50 $\times$ 2.1 mm) Restek (Bellefonte, PA, USA). Mobile phase A consisted of 0.1% formic acid (FA) in water and mobile phase B consisted of 0.1% formic acid in acetonitrile (ACN). The Agilent LC–MSD settings were as follows: positive electrospray mode, capillary voltage 3500 V, drying gas (N_2) 12 l min^{-1} at 350°C , nebulizer gas (N_2) pressure 50 psi, SIM m/z 425 and 393, fragmentor voltage 50 V. The injection volume was 20.0 μl , flow rate was 0.4 ml min^{-1} and the column temperature was 30°C . Total run time was 25 min.

The ivacaftor analytical method was validated according to the European Medicines Agency Guideline on Bioanalytical Method Validation [20]. Plasma samples were spiked with known concentrations of ivacaftor to produce a standard curve from 0.125 $\mu\text{g ml}^{-1}$ to 4 $\mu\text{g ml}^{-1}$. The method was shown to be sufficiently selective down to a

concentration of 0.125 $\mu\text{g ml}^{-1}$ and $1/x^2$ weighting was the simplest model that described the relationship between plasma concentration and instrument response. Inter-day and intra-day accuracy, as represented by mean bias, and precision, as represented by coefficient of variation, were all within 15%. Ivacaftor was shown to be stable for 2 months at -80°C as well as stable at room temperature for at least 6 h.

Plasma standards or thawed study samples were mixed 1:1 with 300 μl of phosphate buffer: 20 μl of internal standard was added to each sample, and 550 μl was then placed on an ISOLUTE® SLE+ Supported Liquid Extraction column and drawn onto the column with the application of a vacuum. After 5 min, columns were washed through with 5 ml of methyl tert-butyl ether. Samples were then blown to dryness and reconstituted with 200 μl of ACN:H₂O 1:1 plus 0.1% FA. This was then centrifuged at $35\,199 \times g$ at 4°C for 10 min to remove any remaining particulate matter. The supernatant was then transferred to Agilent autosampler vials with 150 μl glass inserts. All patient samples were analysed in duplicate.

Pharmacokinetic analysis

The pharmacokinetic parameters for ivacaftor were determined by non-compartmental methods using Phoenix WinNonlin Professional (version 6.4; Pharsight, Mountain View, CA) pharmacokinetic software. Parameters estimated included $\text{AUC}_{0-\text{inf}}$ obs , area under the plasma concentration–time curve over 12 h (AUC_{0-12}), $t_{1/2}$, C_{max} and t_{max} . AUC was calculated using the linear trapezoidal rule. The $t_{1/2}$ of ivacaftor was calculated from at least three terminal concentrations.

Statistical analysis

A sample size of eight was originally calculated to have 90% power to detect a two-fold increase in the half-life of ivacaftor with a type 1 error rate of 5%. To account for a dropout rate of 20% in the context of the sequential crossover design with three sequences and three periods, a sample size of 12 was chosen.

Statistical analysis of both data from the bioanalytical method validation and pharmacokinetic parameters derived from WinNonlin pharmacokinetic software were performed using GraphPad Prism version 6.00 for Windows (GraphPad Software, La Jolla, CA). Individual pharmacokinetic parameters were log transformed and compared between treatments using the Wilcoxon signed-rank test. A P -value of <0.05 was considered significant.

Results

Subject demographics

A total of 12 subjects were enrolled in the study, two of whom were female. The median age of the subjects was 23 years (range 20–30 years), median body weight was 71.25 kg and median body mass index (BMI) was 23.1 kg m^{-2} . All subjects were Caucasian.

Safety and tolerability

Both ivacaftor and ritonavir were well tolerated in the study population. There were no deaths or serious adverse events reported during the study. Mild adverse events reported included nausea in three subjects during the 2 weeks of ritonavir treatment, lasting for 1 day each, coryza in the first 24 h of studies B and C in one subject and numbness in the index finger and thumb of one subject which lasted 5 days during ritonavir treatment for 2 weeks. All adverse events resolved spontaneously and did not require discontinuation of study drug.

Concentration–time profiles of ivacaftor

The median ($\pm$ interquartile range) concentration–time profiles of ivacaftor in studies A, B and C are shown in Figure 2.

Figure 2

Concentration–time profiles of ivacaftor from studies A, B and C (median $\pm$ interquartile range)

Table 1

Summary of PK parameters of ivacaftor in studies A, B and C

	Study A	Study B	Study C	Geometric mean ratio Study A: Study B	Geometric mean ratio Study A: Study C	Geometric mean ratio Study B: Study C
AUC_{0-12} ($\mu\text{g}\cdot\text{hr}\cdot\text{ml}^{-1}$)	7.024 (5.48–9.0)	16.65 (11.4–24.32)	21.5 (17.38–26.59)	2.37 (1.62–3.47)	3.06 (2.36–3.97)	1.29 (0.856–1.95)
$AUC_{0-\text{inf}}$ obv ($\mu\text{g}\cdot\text{hr}\cdot\text{ml}^{-1}$)	10.94 (8.26–14.48)	215.6 (146.4–317.4)	216 (165.5–281.8)	19.71 (13.18–31.33)	19.77 (14.0–27.93)	1.00 (0.68–1.47)
C_{max} (μg)	0.9944 (0.7819–1.265)	1.812 (1.323–2.482)	2.267 (1.863–2.757)	1.82 (1.34–2.48)	2.28 (1.84–2.83)	2.54 (0.65–9.9)
$t_{1/2}$ (h)	7.12 (5.59–9.07)	79.34 (65.5–96.1)	65.99 (57.43–75.82)	11.14 (8.72–13.26)	9.27 (6.68–12.85)	0.83 (0.63–1.1)
Median time to t_{max} (range) (h)	2.5 (2–4)	6.5 (3–23.75)	4.0 (3–10)			

Pharmacokinetic parameters

Ivacaftor pharmacokinetic parameters are summarized in Table 1. Significantly higher exposure to ivacaftor, as represented by $AUC_{0-\text{inf}}$ obv was found when ivacaftor was administered with ritonavir in both studies B and C compared with ivacaftor alone in study A ($P = 0.0005$ and 0.0005 respectively). $AUC_{0-\text{inf}}$ obv (95% CI) was 10.94 (8.259–14.48) $\mu\text{g}\cdot\text{h}\cdot\text{ml}^{-1}$ in study A compared to 215.6 (146.4–317.4) $\mu\text{g}\cdot\text{h}\cdot\text{ml}^{-1}$ in study B and 216 (165.5–281.8) $\mu\text{g}\cdot\text{h}\cdot\text{ml}^{-1}$ in study C, respectively (GMR [95% CI] study A:study B 19.71 [13.18–31.33] and study A:study C 19.77 [14.0–27.92], respectively). C_{max} (GM [95% CI]) in study A was 0.9944 (0.7819–1.265) μg , 1.812 (1.323–2.482) μg in study B and 2.267 (1.863–2.757) μg in study C, respectively. C_{max} of ivacaftor was significantly increased in the presence of ritonavir in both study B and study C (GMR [95% CI] 1.82 [1.34–2.48] and 2.28 [1.84–2.83] respectively; $P = 0.0049$ and 0.0005 respectively) with no significant difference in C_{max} of ivacaftor between study B and study C ($P = 0.2661$). Median t_{max} of ivacaftor was significantly later in the presence of ritonavir (median [range] 2.5 [2–4] h, 6.5 [3–23.75] h and 4 [3–10] h in studies A, B and C, respectively; $P = 0.001$).

Elimination half-life (GM [95% CI]) of ivacaftor in study A was 7.121 (5.59–9.07) h compared to 79.24 (65.5–96.1) h in study B and 65.99 (57.43–75.82) h in study C. The $t_{1/2}$ of ivacaftor was significantly prolonged by coadministration of ritonavir in both study B and study C in comparison to study A (GMR [95% CI] 11.14 [8.72–13.26] and 9.27 [6.68–12.85] respectively; $P = 0.0005$ and 0.0005 respectively). There was no significant difference in $t_{1/2}$ between study B and study C (GMR [95% CI] 0.83[0.63–1.1]; $P = 0.2036$). The coefficient of variation of $AUC_{0-\text{inf}}$ obv and C_{max} was similar between studies A, B and C. The coefficient of variation in $t_{1/2}$ of ivacaftor reduced with the addition of ritonavir, reducing to almost half when comparing study C to study A, as shown in Table 2.

Discussion

The pharmacokinetic data obtained from this healthy-volunteer, drug-interaction study show that ritonavir at a

Table 2

Coefficient of variation (%) of key PK parameters

	Study A	Study B	Study C
$AUC_{0-inf\ obv}$	45.12%	41.86%	45.82%
C_{max}	37.46%	33.13%	34.59%
$t_{1/2}$	43.96%	33.48%	22.32%

dose of 50 mg administered once daily, in both acute and chronic dosing, significantly increases plasma concentrations of ivacaftor (Table 1). All key pharmacokinetic parameters (AUC_{0-12} , $AUC_{0-inf\ obv}$, C_{max} , $t_{1/2}$) were increased several fold by the presence of ritonavir. Additionally, the coefficient of variation of $t_{1/2}$ of ivacaftor was decreased by the use of ritonavir for 2 weeks prior to ivacaftor administration (Table 2). These data provide proof of concept that concomitant dosing of ivacaftor and ritonavir could be used in clinical practice to increase the dosing interval of ivacaftor while also allowing patients to maintain higher plasma levels than with ivacaftor alone at the recommended dose of 150 mg twice daily.

It was a curious finding that the coefficient of variation of C_{max} and $AUC_{0-inf\ obv}$ did not change, while that of $t_{1/2}$ showed a marked reduction. There are insufficient data in the current study to fully explore this phenomenon, though it could be hypothesized that the variability in drug absorption seen in other pharmacokinetic studies on ivacaftor contributed to this [21]. While absorption of ivacaftor may have remained variable with co-administration of ritonavir, thus affecting the variability of C_{max} and $AUC_{0-inf\ obv}$, the variability in elimination was smoothed out, and this was seen in the reduction in variability in $t_{1/2}$.

In the early years of HIV treatment, the use of ritonavir was associated with a number of significant and debilitating side effects such as abdominal pain, nausea, vomiting, severe diarrhoea, paresthesias, rashes and peripheral neuropathy. Doses used for treatment (as opposed to those used for pharmacokinetic enhancement) were up to 1200 mg per day [22]. The side effects of ritonavir used at doses for pharmacokinetic enhancement are reported to be much less frequent and less severe [23]. These side effects have also been shown to be dose related and it was for this reason that the smallest dose of ritonavir reported in the literature to provide significant boosting of other protease inhibitors (50 mg once daily) was used [16, 24]. It was encouraging that no volunteer experienced side effects of ritonavir that compelled them to stop taking the drug, and for those who did experience side effects, these were mild and transient. This suggests that ritonavir will be tolerable for use in pharmacokinetic enhancement of ivacaftor in clinical practice for patients with cystic fibrosis.

A comparison of study B and study C data suggests that similar inhibition is achieved with acute and chronic dosing of ritonavir. This is an important finding, as some drug interactions with ritonavir show change over time.

Alprazolam is one example; one study showed there is significant inhibition of alprazolam metabolism with acute dosing of ritonavir, but when ritonavir was used daily for 12 days, this effect disappeared. It is hypothesized that this was due to the induction effect of ritonavir [25]. It was therefore important to establish that such a situation would not arise with the inhibition of ivacaftor. As the induction effects of ritonavir are maximal at 2 weeks [25] the equivalent level of inhibition that exists between study B and study C suggests that any induction effects of ritonavir will not be clinically significant should ritonavir be used in the long term as a pharmacokinetic enhancer.

The use of pharmacokinetic enhancement of ivacaftor with ritonavir in clinical practice not only has the potential to improve clinical outcomes for people with cystic fibrosis on ivacaftor treatment; increasing the dosing interval would significantly reduce the cost of ivacaftor. The magnitude of the pharmacokinetic enhancement demonstrated by this small dose of ritonavir opens the possibility of much reduced dosing of ivacaftor, such as ivacaftor 150 mg twice *weekly* rather than the current regime of ivacaftor 150 mg twice daily (as is the case in current clinical practice when ketoconazole, another strong CYP inhibitor, is used in conjunction with ivacaftor) [11]. This is a particularly significant finding as ivacaftor is one of the most expensive drugs purchased by the Irish health service: treatment for a small cohort of approximately 130 patients costs almost €30 million per annum [15]. This drug is equally, if not more, expensive in other countries across the globe [26, 27]. Using ritonavir to increase ivacaftor levels in this way means that significant cost savings may be achieved without compromising the clinical effectiveness of the drug.

Current safety data available from early clinical studies show that the increased plasma levels of ivacaftor obtained with co-administration of itraconazole do not result in increased toxicity, offering reassurance that increased plasma levels of ivacaftor resulting from co-administration of ritonavir will not be problematic [7]. Future studies can be carefully designed based on the information gleaned from the current study to explore the ideal ivacaftor plus ritonavir dosing regimen for patients with cystic fibrosis.

Based on the above findings, it appears that ivacaftor metabolism is particularly sensitive to the effects of CYP3A4 inhibitors. This opens the possibility of further studies exploring other inhibitors such as cobicistat, the newly marketed, specifically designed CYP3A4 inhibitor currently used in the treatment of HIV for pharmacokinetic boosting. Therefore, there is potential for a number of boosting agents to become available to patients on high-cost drugs such as ivacaftor in the future.

As we move into an era of ultra-high-cost drugs for orphan diseases, we need innovative solutions to overcome the challenges of providing healthcare that is both equitable and at an acceptable opportunity cost. The potential benefits of using a CYP3A4 inhibitor in the CF setting warrants exploration given the proof of the concept that ivacaftor plasma levels can be significantly increased with the use of a small dose of ritonavir.

Competing Interests

There are no competing interests to declare.

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Contributors

Author responsibilities were as follows: A.M.L., G.M.L., S.S., D.M.D. and M.G.B. all contributed to the preparation of the manuscript. A.M.L., S.S. and M.B. designed the research. A.M.L. performed the clinical research and was principal investigator of the clinical trial. G.M.L. and A.M.L. developed the LC–MS assay, and data analysis and interpretation were undertaken by A.M.L., S.S., D.M.D. and M.B. All authors approved the final version of the manuscript.

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