Published in final edited form as:

Pediatr Pulmonol. 2018 May ; 53(5): E6–E8. doi:10.1002/ppul.23971.

Sensitivity of ivacaftor to drug-drug interactions with rifampin, a cytochrome P450 3A4 inducer

Jennifer S. Guimbellot^{1,2,*}, Edward P. Acosta^{1,3}, and Steven M. Rowe^{1,2,4}

¹Gregory Fleming James Cystic Fibrosis Research Center, University of Alabama at Birmingham (UAB), Birmingham, AL

²Department of Pediatrics, Division of Pulmonary and Sleep Medicine, UAB, Birmingham, AL

³Department of Pharmacology and Toxicology, UAB, Birmingham, AL

⁴Departments of Medicine and Cell Developmental and Integrative Biology, UAB, Birmingham, AL

Abstract

The CFTR potentiator ivacaftor is responsible for significant clinical improvements among a subset of patients with cystic fibrosis. Because it is a substrate of the cytochrome P450 system, specifically CYP3A4/5, ivacaftor is subject to significant drug-drug interactions, including due to commonly used antimicrobials such as rifampin. While the interaction of rifampin and ivacaftor has been examined *in vitro*, severe adverse events resulting from this interaction have not been reported in the literature. In this report, we describe the termination of steady, long-term improvement in a patient taking ivacaftor, resulting from the use of rifampin and precipitating a significant pulmonary exacerbation.

Keywords

ivacaftor; CFTR; rifampin; drug-drug interaction; cytochrome P450

Introduction:

The treatment of some patients with cystic fibrosis (CF) has been transformed by the advent of the small molecule CFTR potentiator, ivacaftor, resulting in significant improvements in lung function, exacerbation frequency, quality of life, and disease progression. Currently, ivacaftor is indicated as monotherapy for 38 different mutations (out of approximately 1900 known *CFTR* variants). Ivacaftor is also part of two different combination therapy regimens (ivacaftor / lumacaftor, and ivacaftor / tezacaftor) for other CF patients and may be efficacious in patients with COPD and chronic bronchitis¹. Ivacaftor is a substrate of the

*Corresponding Author: jguimbellot@pediatrics.uab.edu, University of Alabama at Birmingham, Department of Pediatrics, Pediatric Pulmonary & Sleep Medicine, Lowder Building, Suite 620, 1600 7th Avenue South, Birmingham, AL 35233, Phone: (205) 234-0250, Fax: (205-975-5983).

Author contributions: JSG and SMR drafted the manuscript and figures; EPA provided critical revisions. All authors approved the final version of the manuscript.

Declaration of competing interests: SMR serves as an investigator and consultant to Vertex Pharmaceuticals, the manufacturer of ivacaftor, on the design and conduct of CF clinical trials. All other authors declare no conflicts of interest.

cytochrome P450 system, with the potential for multiple drug-drug interactions, a critical issue given the multi-drug regimens most CF patients are prescribed.

Here, we present a patient with cystic fibrosis who was prescribed rifampin, a potent inducer of cytochrome P450 3A4, as part of an antimicrobial regimen while still taking ivacaftor. This case demonstrates the sensitivity of ivacaftor to drug-drug interactions causing a pronounced impact on patient outcome.

Case:

A 27-year-old female with cystic fibrosis (G551D/F508del) initiated ivacaftor during clinical trials as an adolescent, enrolling in the Phase III randomized controlled trial, followed by open-label extension, and then commercial ivacaftor. She reported dramatic symptomatic improvement upon its initiation, with improvement from 61% to 73% absolute percent predicted forced expiratory lung volume in 1 second (ppFEV1) over ~6 years (Figure 1B) and increased weight of 1.6 kg/year (Figure 1C). She had 2 hospitalizations and 3 outpatient exacerbations in the two years prior to the open-label extension, whereas subsequent to ivacaftor, she had 3 mild outpatient exacerbations in 6 years. These considerable improvements were achieved despite increasing non-adherence to other chronic respiratory and nutritional therapies (cessation of pancreatic enzyme supplementation for 4–5 years; reduced inhaled therapies except dornase alpha). She was colonized with *Pseudomonas aeruginosa* for over 10 years, and frequently isolated Methicillin-sensitive *Staphylococcus aureus* and *Haemophilus parainfluenzae* from routine respiratory cultures. For the last two years, she isolated *Mycobacterium abscessus*, but the patient declined aggressive antimicrobial treatment. During this time, her weight and ppFEV1 continued to improve and she deferred appointments to the cystic fibrosis clinic due to her clinical stability.

At the index clinical visit, she reported no significant symptoms, although she experienced a decline in ppFEV1 from 71 to 64 ppFEV1 at two visits over one year. Her weight declined 5.8 kg to 55.4 kg (reflecting a BMI of 21 kg/m²), although the patient reported this was induced by lifestyle changes. Sputum culture revealed new growth of methicillin-resistant *S. aureus*. Her decline in ppFEV1 and weight were attributed to acquisition of MRSA and suboptimal compliance with therapies (although she had been non-adherent for several years). An anti-staphylococcal treatment regimen was initiated to treat MRSA and improve lung function. Because she was severely allergic to sulfa drugs, doxycycline was selected. The prescriber preferred to add rifampin to enhance MRSA clearance, since the combination of the two was considered more effective than doxycycline alone.

Within two days initiating therapy, the patient complained of increased productive cough, dyspnea, and abdominal pain. Upon return to clinic shortly after completing the four week antibiotic course, her ppFEV1 had declined to 55% from prior value of 64%. Her weight declined one kg further to 53.6 kg. Sputum culture was positive for *P. aeruginosa*, MRSA, and *M. abscessus*. Although admission to the hospital for intensification of therapies was recommended, she declined in favor of outpatient therapy. She was initiated on oral linezolid and ciprofloxacin for two weeks, to address MRSA and *P. aeruginosa*. Pulmonary function testing one month after completion of antibiotic treatment showed a ppFEV1 of 71%. Since

that time, her weight (57.2 kg) and lung function (ppFEV1 63%) three months later have remained stable, although at a lower baseline.

Discussion:

In this patient, ivacaftor resulted in substantial improvements despite poor adherence to recommended therapies and the isolation of *M. abscessus*. Her excellent progress terminated with acquisition of MRSA and treatment with rifampin. While some decline in her clinical status was noted prior to initiation of rifampin, and may be partially attributed to MRSA, the use of rifampin (known to potently and strongly accelerate the metabolism of ivacaftor) induced a rapid deterioration in symptoms which were not present prior to its initiation, precipitating her first significant pulmonary exacerbation in several years. This event is considered to be an under-appreciation of the clinical impact of this important drug-drug interaction, as it contributed to loss of lung function and weight from which the patient has not yet completely recovered, as can be seen with abrupt ivacaftor withdrawal.²

Ivacaftor is a substrate of cytochrome P450 enzymes (CYP3A4 and CYP3A5, Figure 1A)^{3,4}. When metabolized by CYP3A4/5, metabolites are produced with reduced or absent activity: M1 (hydroxymethyl-ivacaftor) and M6 (ivacaftor-carboxylate)⁴. Because of the prevalence of drugs metabolized by these enzymes, drug-drug interactions with ivacaftor are a significant and sometimes under-recognized concern. Rifampin is a potent inducer of the CYP3A isoforms and P-glycoprotein^{3,4}, and as such should not be taken concomitantly with ivacaftor as it would be expected to reduce the concentration of the parent drug in the target tissues. However, it is also a key component of CF antimicrobial therapies. For the treatment of methicillin-resistant *S. aureus*, rifampin has excellent penetration into airway secretions and the intracellular compartment, and is often used to augment the effect of other antimicrobials, particularly in the presence of sulfa allergy or concern of small colony variants. If the infection rate of non-tuberculous mycobacterium continues to rise, including *M. avium* complex, the use of rifampin in combination with other antimicrobials may increase among CF patients.

The effect of concurrent administration of rifampin with ivacaftor has been shown in preclinical studies, suggesting that co-administration would result in a nine-fold decrease in the area-under-the curve (AUC, a measure of drug exposure in pharmacokinetic studies) of ivacaftor.³ This is the first case report of an adverse clinical outcome occurring in a patient after initiation of rifampin, validating the risk of adverse patient outcomes from co-administration of these drugs. There is also evidence that a sudden drop in circulating ivacaftor concentrations can precipitate severe pulmonary exacerbation². In our case, the potent induction of ivacaftor metabolism by rifampin likely resulted in rapidly lower drug concentrations and diminished lung function. This illustrates the potential risk of such drug-drug interactions, and that clinical outcomes of patients may be dramatically altered when they are encountered.

Acknowledgements and Role of the funding source:

SMR and JSG are supported by the NIH (R35HL135816 and DK072482 to S.M.R.), and the Cystic Fibrosis Foundation. The funding sources provided no input to the content of the manuscript.

Acknowledgements: W. Scott House and Ginger Reeves assisted with data collection.

Abbreviations:

CF	cystic fibrosis
CFTR	Cystic Fibrosis Transmembrane conductance regulator
ppFEV1	percent predicted forced expiratory volume in one second
COPD	chronic obstructive pulmonary disease

References:

1. Solomon GM, Hathorne H, Liu B, Raju SV, Reeves G, Acosta EP, Dransfield MT, Rowe SM. Pilot evaluation of ivacaftor for chronic bronchitis. *Lancet Respir Med* 2016;4(6):e32–3. [PubMed: 27185048]
2. Trimble AT, Donaldson SH. Ivacaftor withdrawal syndrome in cystic fibrosis patients with the G551D mutation. *J Cyst Fibros* 2017.
3. Jordan CL, Noah TL, Henry MM. Therapeutic challenges posed by critical drug-drug interactions in cystic fibrosis. *Pediatr Pulmonol* 2016;51(S44):S61–S70. [PubMed: 27662106]
4. Robertson SM, Luo X, Dubey N, Li C, Chavan AB, Gilmartin GS, Higgins M, Mahnke L. Clinical drug-drug interaction assessment of ivacaftor as a potential inhibitor of cytochrome P450 and P-glycoprotein. *J Clin Pharmacol* 2015;55(1):56–62. [PubMed: 25103957]

Figure 1. Induction of drug metabolism by rifampin results in altered ivacaftor effects.

A. Diagram demonstrating that rifampin induces CYP3A4 and CYP3A5, resulting in increased metabolism of ivacaftor to less active metabolites (left panel); in comparison, a lack of CYP3A4 and CYP3A5 function yields a high level of ivacaftor inside the cell to increase open probability of ivacaftor (middle panel); some activity of the enzymes result in “typical” metabolism of ivacaftor (right panel). B-C. Percent predicted FEV1 and weight are shown; for each outcome, the average value per year is shown. The first vertical dotted line represents the start of randomized controlled trial followed by continuous ivacaftor administration, and the second dotted line initiation of rifampin, which continued for one month. The downward red triangles are the values just after rifampin was completed, whereas the upward green arrows are the values after several weeks of unopposed ivacaftor treatment. Cl⁻ (chloride); iva (ivacaftor); Rif (Rifampin).