Cystic Fibrosis: A Novel Pharmacologic Approach to Cystic Fibrosis Transmembrane Regulator Modulation Therapy

Deborah Virant-Young, PharmD; Justin Thomas, DO; Sarah Woiderski, DO; Michelle Powers, OMS III; Joseph Carlier, MA, OMS III; James McCarty, OMS III; Tyler Kupchick, OMS III; and Anthony Larder, OMS III

From the Department of Pharmacology and Toxicology (Dr Virant-Young) at the Michigan State University College of Osteopathic Medicine in East Lansing (Drs Thomas and Woiderski, Ms Powers, and Mr Carlier, Mr McCarty, Mr Kupchick, and Mr Larder); the Department of Neurological Surgery at St John Providence Hospital and Medical Center in Southfield, Michigan (Dr Thomas); and the Department of Internal Medicine at Huron Valley-Sinai Hospital, in Commerce, Michigan (Dr Woiderski). Dr Virant-Young is certified by the Board of Pharmacy Specialties.

Financial Disclosures: None reported.

Support: None reported.

Address correspondence to Deborah Virant-Young, PharmD, 44575 Garfield Rd, Clinton Township, MI 48038-1139.

E-mail: deborah.young@hc.msu.edu

Submitted January 20, 2015; revision received April 27, 2015; accepted June 8, 2015.

Therapy for cystic fibrosis (CF) has progressed during the past several decades. Much of this progress is because of advances in genetic testing to precisely identify the underlying cause of CF transmembrane regulator (CFTR) dysfunction. However, with more than 1900 mutations that can produce a faulty CFTR, the management of CF can remain a challenge. Several innovative drugs recently approved by the Food and Drug Administration, termed genetic modulators, target the underlying disease by modulating the CFTR defect. This review provides physicians with an established simple classification scheme to guide their use of these drugs. The treatment challenge of 1900 CFTR mutations has been simplified into 6 physiologic classes, each paired with an available therapy to offer patients the most functional improvement. Drug therapy monitoring, adverse effects, and indications for discontinuation must also be considered.

J Am Osteopath Assoc. 2015;115(9):546-555
doi:10.7556/jaoa.2015.112

Cystic fibrosis (CF) is an autosomal recessive disease affecting more than 30,000 individuals in the United States and approximately 70,000 individuals worldwide.[1-4] It is most common in white persons, specifically Europeans and those with Ashkenazi Jewish ancestry.[5] It affects 1 in 3,000 live births among white persons and 1 in 17,000 live births among African American persons; it is rarely present in Native American or Asian populations.[2,5] The life expectancy during the 1960's did not surpass the single digits.[6] With antibiotic and symptomatic intervention now available for CF patients at an early age, the life expectancy for an individual with CF has increased substantially; in 2013, predicted median survival was reported to be 41 years.[1] Unfortunately, no cure exists for CF, and, until recently, therapies have been directed only at its associated symptoms and complications.

The central theme to CF is an absent or dysfunctional CF transmembrane regulator (CFTR), a vital chloride ion transporter in multiple organs that controls the regulation of epithelial sodium transport. A diseased CFTR leads to dilatation of exocrine glands (from mucus obstruction and thick, productive mucopurulent secretions) accompanied by submucosal glandular hyperplasia. The result is multiorgan damage caused by ion, pH, and fluid imbalances.[2,7] Many patients present at birth with meconium ileus and pancreatic insufficiency due to small-bowel and pancreatic mucus obstruction, respectively.[2] In the pulmonary system, chloride ion and fluid imbalance lead to destruction of respiratory cilia, thick mucus collection in the distal airways, and, inevitably, progressive obstructive lung disease. Bacterial colonization of the respiratory tract, most notably from *Pseudomonas aeruginosa*, *Burkholderia cepacia*, and *Staphylococcus aureus*, is a major cause of disease and death associated with chronic pulmonary infections.

As of 2011, more than 1900 mutations have been identified that may clinically manifest as CF, and approximately 1 in 25 white persons are carriers of a CF genetic mutation (though most who are heterozygous for these mutations do not present with CF).[8] These mutations compromise the integrity of the CFTR protein located on the outer membrane of epithelial cells.[8] Therefore, the most important organ systems affected by CF are those in which fluid and electrolyte balance by epithelial cells is critical, such as the airways, exocrine glands of the pancreas, bile ducts, and sweat glands.

A classification system[9] was devised and classified in 6 classes based on molecular mechanisms and consequences that the mutation causes (*Table 1*), which are as follows: no synthesis of CFTR (class I), premature degradation (class II), dysregulation (class III), abnormal conductance (class IV), decreased production (class V), and membrane instability (class VI).[2,7,8,10,11] Recent therapies have shifted toward treating classes of *CFTR* mutations rather than allele-specific mutations.[11] This classification has become useful outside the research community and pharmaceutical industry because individual therapies are effective only in patients with a particular class of *CFTR* mutation.

A major challenge in managing CF is the need to tailor individualized therapy for nearly every patient based on his or her genomic mutation. With several new therapies developed for these mutations, a shift toward managing the underlying disease rather than just managing symptoms is currently underway. Ivacaftor (VX-770) was the first of these genetic modulators to be approved by the US Food and Drug Administration (FDA), for the treatment of patients with a class III defect. Several other therapies have since been introduced for the clinical management of CF. In this review, we provide an overview of the genetic modulators currently available, using the classification system for defects to organize treatment options. We also describe several new drugs designed to correct the underlying genetic mutations in CF.

Class I Defects

Class I defects account for single point mutations in DNA that inappropriately place a stop codon in the CFTR messenger RNA (mRNA) transcript and terminate the process of translation. The CFTR protein is left truncated, resulting in a loss of function at the apical layer of epithelial cells. These mutations are present in approximately 10% of patients with CF worldwide, and several novel therapies have been developed to target this specific population.[11]

Tobramycin (Tobi; Novartis) is the bactericidal aminoglycoside antibiotic most commonly used today for coverage against severe gram-negative respiratory infections (eg, *P aeruginosa* infection) in patients with CF.[13] Its mechanism is to interfere with bacterial proteins by binding to the 30S ribosomal RNA subunit during protein translation. Recent evidence suggests that aminoglycoside antibiotics can suppress premature termination codons by disrupting translational fidelity and allowing translation to continue to the normal termination of the transcript.[13] Aminoglycosides have additional dose-dependent pleiotropic effects whereby they induce "read-through" of premature stop codons, suppressing a premature stop codon and restoring synthesis to a full-length and functional CFTR protein.[14,15] Aminoglycoside binding to the ribosome enables read-through inducing misinterpretation of a stop codon, so that ultimately the stop codon directive is "ignored."[16,17]

Gentamicin was the first aminoglycoside investigated for this function.[14,15] Ex vivo administration of gentamicin was shown to increase CFTR function. In 2003, a double-blind, placebo-controlled trial[12] evaluated the use of topical nasal drops (gentamicin dose, 900 µg/d) to improve nasal respiratory function. This application significantly reduced the basal potential difference of nasal epithelium in both homozygous and heterozygous patients (n=19) with a stop codon defect (P=.005).[7,12] Homozygous carriers of a nonsense mutation had a greater response to gentamicin, with

Table 1.
Classification and Available Therapies for CFTR Gene Mutations[5-9]

	Class I	Class II	Class III	Class IV	Class V	Class VI
Defect of CFTR	No synthesis	Mistrafficking; degradation in endoplasmic reticulum/Golgi	Dysregulation; no response to ATP or cAMP	Low functioning gating; reduced Cl– ion transport	Low production; splicing defect with reduced production	Membrane instability
Sequelae of CFTR defect	Premature stop codon placement in CFTR mRNA or splicing defect	Misfolded CFTR	Gating mutation	Channel narrowing	Transportation of chloride does occur	Conductance of ions other than chloride are impaired
Functional CFTR present	No	No	No	Yes	Yes	No
Mutation Examples	G542X, W1282X, R553X, ΔT3950	ΔF508, N1303K	G551DR117H,	R334W, G314E, R347P, D1152H	3849+10 kbC→T, 2789+5G→A 3272-26A→G	1811+1.6 kb A→G
Approximate prevalence in patients with CF[a,8]	9%	89%	4%	2%	3%	Unknown
Available gene Modulating Therapies	Ataluren (PTC-124) gentamicin	Lumacaftor (VX-809) ivacaftor[b]	Ivacaftor (VX-770)	Ivacaftor[b] (VX-770)	None	None

[a] Approximate percentages of CFTR (cystic fibrosis transmembrane regulator) mutations do not equal 100% as many individuals have multiple mutations.
[b] Currently under investigation

Abbreviations: ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; Cl–, chloride.

apical CFTR function fully restored to nasal epithelial tissue in approximately 90% of patients. However, the high dosage needed to produce a clinically significant effect on chloride transport during systemic administration was a major limitation to the use of gentamicin (and other aminoglycosides). Although gentamicin has the pharmacologic potential to resolve several issues in CF, the required therapeutic dose has many toxic effects associated with long-term use, most notably renal and otovestibular effects.[11,12]

At this publication, gentamicin and other aminoglycosides are not approved by the FDA for the sole purpose of CFTR modulation. However, many individuals with CF are treated with aminoglycosides (specifically tobramycin) for gram-negative pulmonary infections and not solely for modification of mutations.[13] Many physicians consider tobramycin the aminoglycoside of choice for managing lung infections associated with CF, with its pleiotropic effect in promoting CFTR modulation. We recommend using standard aminoglycoside dosing practices to manage the lung infections associated with CF, along with monitoring for renal toxic effects.

Ataluren (PTC 124; PTC Therapeutics),[18] currently recognized as an orphan drug by the FDA, is a more appealing therapeutic option for class I CFTR defects. In a mechanism similar to the pleiotropic effects of aminoglycosides, ataluren allows ribosomes to read

through the mRNA premature stop codons, resulting in the translation of complete CFTR proteins.[19,20] Several phase II and III studies[19-21] have evaluated this drug's efficacy and demonstrated improvements in nasal transepithelial potential differences, forced expiratory volume in 1 second (FEV_1), and weight gain in both adult and pediatric patient populations.[20] Adverse effects were generally mild, with gastrointestinal upset, headache, and dizziness most commonly reported (*Table 2*). Because of its efficacy in targeting the underlying cause of CF and favorable adverse effect profile, ataluren is considered the more appropriate initial approach compared with aminoglycosides in patients with CF who have class I mutations.[10,21] Several phase III trials of ataluren are currently underway in patients with CF who are aged 6 years or older, to determine long-term safety and efficacy (*Table 3*).[1,20] One phase III trial found that combining ataluren with tobramycin may reduce its efficacy, suggesting that this combination should not be used.[22] Another antibiotic would therefore need to replace tobramycin should a gram-negative infection develop in a patient receiving ataluren. In these situations, ideal antibiotic therapy would be based on culture and sensitivity results.

Class II Defects

Class II defects of CFTR are present in 90% of all patients with CF (*Table 1*). Patients with class II defects have a deletion of the amino acid phenylalanine at the 508 position (ΔF508), resulting in immature synthesis of the CF channel protein. The CFTR is only partially glycosylated and subsequently not released correctly from the endoplasmic reticulum. The structural errors are then recognized by the ubiquitin-proteasome system, and the abnormal CFTR protein is eventually degraded.[10] To counteract this error, lumacaftor (VX-809; Vertex Pharmaceuticals; phase II trials complete)[23-26] modulates function to ΔF508-*CFTR* mutations by restoring the posttranslational modification at the endoplasmic reticulum. By avoiding degradation from ubiquitin and enhancing chloride ion secretion in bronchial epithelial cells, lumacaftor helps correct a ΔF508 mutation in patients with a class II defect and has been shown to increase CFTR chloride transport by 15% above baseline.[23-26]

Measurement of sweat chloride concentrations in a randomized, double-blind, placebo-controlled trial[25] demonstrated statistically significant (P=.0013) and sustained improvements in patients taking lumacaftor; these effects were dose dependent, with reductions of 6.1 and 8.2 mmol/L in sweat chloride concentrations after 28 days of therapy with daily lumacaftor doses of 100 mg and 200 mg, respectively. After discontinuation of the drug, however, this effect was rapidly reversed, suggesting that lumacaftor is bioactive and should be therapeutically maintained for an adequate clinical effect.[25] Additional research is currently underway to evaluate bioactivity and dosing regimens, because no ideal regimen has yet been established. Results reported for varying doses suggest that no significant difference has been found in adverse effects between therapeutic and placebo groups (*Table 4*); the most common adverse effects were headache and cough, with 4 of 89 patients (5%) in 1 study reporting severe pulmonary adverse effects that warranted discontinuation of the drug.[25]

Class III Defects

Normal CFTR function requires the recognition of adenosine triphosphate or cyclic adenosine monophosphate at the CFTR channel. Class III defects occur when this detection is absent.[5] The most common mutation that underlies this defect is a missense mutation of the amino acid glycine for aspartate at the 551 position (G551D) on the CFTR protein.[5] Potentiators amplify ion function by increasing the time that CFTR channels at the cell surface remain open, thereby addressing the class III defect.[2,3] The resultant downstream effect increases both the apical fluid height of epithelium and the ciliary

Table 2.
Adverse Effect Profile of Ataluren in Patients With CF Class I Mutations[a,14]

	Adverse Effect, No. (%)					
Treatment	CF Pulmonary Exacerbation[b]	Dysuria	Abdominal Pain	Diarrhea	Constipation Without Obstruction	Notes
First cycle (n=23)[c] Dose: 4 mg/kg 3 times daily with meals Duration:14 d discontinued followed by 14 d without treatment	2 (8.7)	4 (17.4)	3 (13)	2 (8.7)	NA	Mild/moderate; not affected by dose; undifferentiated from CF complications; no patient treatment
Second cycle (n=22) Dose: 10 mg/kg at breakfast 10 mg/kg at lunch 20 mg/kg at dinner discontinued Duration: 14 d followed by 14 d without treatment	2 (9.1)	2 (9.1)	2 (9.1)	3 (13.6)	2 (9.1)	Mild/moderate; not affected by dose; undifferentiated from CF complications; no patient treatment

[a] Recommendations: 10 mg/kg at breakfast, 10 mg/kg at lunch, and 20 mg/kg at dinner. Duration of therapy is still under investigation15 at time of publication (Phase III trials). Patients should be monitored for reversible increases in serum creatinine if ataluren is used concomitantly with other nephrotoxic medications.
[b] One patient did not need treatment, and the other was treated with ciprofloxacin.
[c] The CF (cystic fibrosis)–related pulmonary exacerbations were not believed to be caused by ataluren administration. One patient experienced an onset of symptoms before receiving ataluren and was treated with amikacin. Another patient was removed from the study owing to a chronic infection of *Mycobacterium abscessus*.

beat frequency to restore function to a defective cilia transport system in epithelial cells, most notably in the respiratory tract. Ivacaftor (VX-770; Kalydeco–Vertex Pharmaceuticals) has been approved by the FDA as a CFTR potentiator for G551D *CFTR* gating mutations, as well as many other gating mutations in patients aged 6 years or older (*Table 5*).[27-29]

In a randomized, double-blind, placebo-controlled trial[26] of ivacaftor, 84 patients aged 12 years or older with at least 1 G551D *CFTR* mutation and an FEV_1 of 40% to 90% were treated with ivacaftor for 48 weeks. After 24 weeks, the predicted FEV_1 values of patients in the ivacaftor group showed absolute increases from baseline of 10.4% vs absolute decrease of 0.2% for the placebo group. Thus, the treatment effect was 10.6% corresponding with an increase in FEV_1 of 367 mL. These findings corresponded to a 10-fold increase in CFTR-mediated chloride transport in patients with CF and G551D mutations.[29] At the end of the study, patients treated with ivacaftor were 55% less likely to have a pulmonary exacerbation. Respiratory symptoms scored in a CF questionnaire were 8.6 points higher (ie, improved function) (score changes of >4 points were considered clinically significant) in the treatment group than in the placebo group, and treated patients had an average weight gain of 2.7 kg (5.94 lb) more than those

Table 3.
Clinical Trials and Status at Time of Publication for *CFTR* Gene Modulation Therapies[a]

Therapy	Clinical Trial	Phase	Anticipated Completion
Class I			
Ataluren (PTC124)	Efficacy and safety study of PTC124 as an oral treatment for nonsense-mutation-mediated CF	3	Completed
	Extension study of ataluren in patients with nonsense-mutation-mediated CF	3	Completed
Class II			
VX-809	Study of lumacaftor in combination with ivacaftor in patients with CF aged 12 years and older who are homozygous for the F508del-CFTR mutation (TRAFFIC and TRANSPORT studies)	3	Completed
	Study of VX-809 alone and in combination with VX-770 in patients with CF homozygous or heterozygous for the F508del-CFTR mutation	2	Completed No published results at time of publication
VX-661	Study of VX-661 alone and in combination with VX-770 in patients homozygous to the F508del-CFTR mutation	2	Completed No published results at time of publication
	Study to Evaluate Safety and Efficacy of VX-661 in combination with ivacaftor in patients with CF, homozygous for the F508del-CFTR mutation with an open-label expansion	2	July 2015
N6022	Safety and pharmacokinetics study of N6022 in patients with CF homozygous for F508del-CFTR mutation (SNO-1)	1b	Completed Results pending
Class III			
Ivacaftor	VX-770 expanded access program	3	
	Study of ivacaftor in patients with CF who have the R117H-CFTR mutation	3	Completed Results pending
	Study of ivacaftor in patients with CF who have a non-G551D CFTR gating mutation	3	Completed Results pending
	Study of ivacaftor in patients with CF aged 2 through 5 years with a CTFR gating mutation	3	Completed No results posted
	Rollover study of ivacaftor in patients with CF and a non G551D CFTR mutation	3	July 2016
	An open-label, rollover study to evaluate the long-term safety and efficacy of VX-770 in patients with CF	3	Completed
	Study of ivacaftor in patients with CF aged 12 years and older homozygous for the F508del-CFTR mutation (DISCOVER)	2	Completed Results pending

[a] Reproduced from www.clinicaltrials.gov (accessed January 11, 2015).

Abbreviations: CF, cystic fibrosis; CFTR, CF transmembrane regulator.

Table 4.
Adverse Effect Profile of Lumacaftor for Patients With Cystic Fibrosis Class II Mutations[a,24]

Treatment	Adverse Effect[b]	No. (%)[c]
25 mg, for 28 d (n=18)	Cough	10 (55.6)
	Rales	6 (33.3)
	Dyspnea	5 (27.8)
50 mg, for 28 d (n=18)	Cough	6 (33.3)
	Headache	5 (27.8)
	Wheezing	4 (22.2)
100 mg, for 28 d (n=17)	Cough	7 (41.2)
	Productive cough	4 (23.5)
	Upper respiratory tract infection	3 (17.6)
200 mg, for 28 d (n=19)	Cough	10 (52.6)
	Productive cough	6 (31.6)
	Fever	5 (26.3)
	Headache	5 (26.3)
Placebo (n=17)	Cough	7 (41.2)
	Headache	3 (17.6)
	Productive cough	3 (17.6)
	Nasal congestion	3 (17.6)
	Wheezing	3 (17.6)
	Diarrhea	3 (17.6)

[a] Four patients withdrew, 1 in each of the VX-809 groups, owing to adverse respiratory events.
[b] Overall similar occurrence of pulmonary exacerbations between VX-809 and placebo-treated patients.
[c] Dose groups had comparable adverse effect profiles.

treated with placebo. Most notably, ivacaftor was the first therapeutic agent to reduce sweat chloride levels below diagnostic thresholds (60 mmol/L), with these concentrations decreasing by a mean of 48.1 mmol/L in treated patients with G551D *CFTR* mutations, a change correlated with clinical outcome (eg, lung function).[27,31]

The ivacaftor group in that study had a lower proportion of serious adverse events (24% vs 48% in patients receiving placebo); the most common adverse effects were headache, oropharyngeal pain, and upper respiratory tract infections (*Table 5*).[27,28] Ivacaftor is metabolized via the cytochrome P450 3A system into 2 metabolites: a slightly active one (one-sixth the potency of its parent compound) and an inactive one with 88% eliminated by fecal excretion. Because elevated levels of liver function enzymes have been noted, it has been recommended to screen for elevated aspartate aminotransferase and alanine aminotransferase levels before initiating treatment, every 3 months during the first year of treatment, and annually thereafter; elevated levels do not necessarily mean that ivacaftor should be discontinued, but levels should be monitored. Animal studies have shown that ivacaftor does cross the placenta, but no adequate human studies of effects on pregnant women are available, placing the current pregnancy classification as category B.[28]

Studies are also currently underway to evaluate combination therapy. Several phase II trials have demonstrated improvements in FEV_1 and up to a 2-fold reduction in sweat chloride with lumicaftor/ivacaftor combination therapy compared with lumicaftor alone.[24] The results of the TRAFFIC and TRANSPORT trails that studied Lumacaftor in combination with Ivacaftor in patients 12 years of age or older who are homozygous for ΔF508-*CFTR* mutation showed percent predicted FEV_1 improvement ranging from 2.6% to 4.0% ($P \leq .001$) from baseline compared to placebo with improvements sustained over 24 weeks.[32] There was a mean relative improvement for the Lumacaftor/Ivacaftor treatment group of 4.3% to 6.7% ($P \leq .001$) compared with placebo ($P < .001$). In vitro research has shown that when lumacaftor and ivacaftor are used in combination, the chloride transport increases to 30%.[26] The most common adverse events reported were infective pulmonary exacerbations, cough, headache, and increased sputum, but the combination therapy was generally well tolerated (*Table 6*).[33] Phase III trials are currently planned to evaluate dosing regimens for peak efficacy.[20]

Other class III genetic modulators currently being evaluated include VX-661 (Vertex Pharmaceuticals), N6022 (N30 Pharmaceuticals), and C18 (another class III CFTR corrector under investigation). A study[34]

evaluating the effects of lumacaftor and C18 therapy on the ΔF508 mutation has found that this combination can both enhance activation of ΔF508-CFTR and correct the associated folding defect. A phase II study evaluating VX-661 both alone and in combination with ivacaftor is still underway.[35] Other pending studies aim to increase effectiveness with drugs such as N6022 or drug combinations (lumacaftor with ivacaftor or VX-661), without increasing adverse effects.[24,35]

Class IV, V, and VI Defects

Mutations to the *CFTR* gene that involve low function, low production, or membrane instability (class IV, V, and VI defects, respectively) are seen in less than 10% of patients with CF.[9] Most research on CFTR modulation therapy has targeted gene mutations most commonly seen in clinical practice, with research in other classes neglected.

Class IV defects produce an abnormal CFTR protein at the outer membrane of epithelial cells, in which the gating/chloride channels do not function properly. In an experimental phase III study to evaluate its efficacy in patients with CF with the R117H-*CFTR* mutation, ivacaftor improved CFTR channel function and lung function, reduced pulmonary exacerbations and respiratory symptoms, and increased weight gain; it was also well tolerated.[36]

Class V defects have a functional CFTR present, but a splicing defect of mRNA results in a variable phenotype. The severity of disease in patients with class V defects has been postulated to be inversely related to the level of correctly spliced transcripts. Effective therapies would probably include a method to increase mRNA expression, and several compounds are currently under early investigation.[10]

In the past 15 years, evidence has suggested that membrane conductance defects caused by ions other than chloride may also potentiate CFTR dysfunction by leading to membrane instability (class VI defects).[11,37]

Table 5.
Adverse Effect Profile of Ivacaftor for Patients With Cystic Fibrosis Class III Mutations[ab,27]

	Treatment	
Adverse Effect	**Ivacaftor[c]**	**Placebo[d]**
Cough	34 (30.4)	4 (14.3)
Pulmonary exacerbation	25 (22.3)	11 (39.3)
Nasal congestion	13 (11.6)	0
Oropharyngeal pain	0	3 (10.7)
Fatigue	0	3 (10.7)

[a] Data are given as No. (%).
[b] Recommendations: 150 mg every 12 h with fat-containing food of continuous duration. Liver enzymes (alanine aminotransferase, aspartate aminotransferase) should be monitored before initiations every 3 mo for the first year and yearly thereafter.
[c] Part A: 150 mg twice daily for 16 wk (n=112).
Part B: Open-label, 150 mg twice daily up to 96 weeks.
[d] Part A: 16-wk treatment (n=28).

Truncation of the C-terminus of the primary CFTR protein structure may trigger this mechanism and has been a target of several therapies; however, little clinical evidence has supported this approach.[11]

Conclusion

The standards for managing CF have changed considerably during the past 2 decades. Current therapies target the underlying disease by modulating *CFTR* mutations, which are divided into 6 categories (classes): no synthesis (I), premature degradation (II), dysregulation (III), abnormal conductance (IV), decreased production (V), and membrane instability (VI). Recommendations on CFTR modulation therapy for CF have remained elusive for several years despite continuing pharmacotherapeutic advances. This challenge is due in part to the large number of mutations that can lead to CF. Further research is needed in patients of different ethnicities and races to support a comprehensive understanding of the effects of treatment.

Table 6.
Adverse Effect Profile and Most Common Adverse Effects of Lumacaftor + Ivacaftor for Patients With Cystic Fibrosis Class II Mutations as Reported by TRAFFIC and TRANSPORT Studies[a,b]

Safety Data	Placebo	Lumacaftor (600 mg/d) + Ivacaftor (250 mg/12 h)	Lumacaftor (400 mg/d) + Ivacaftor (250 mg/12 h)
Patients with any adverse effect	355 (96)	356 (97)	351 (95)
Patients who discontinued treatment owing to adverse effect	6 (1.6)	14 (3.8)	17 (4.6)
Patients with serious adverse effects	106 (29)	84 (23)	64 (17)
Infective pulmonary exacerbation	182 (49)	145 (39)	132 (36)
Cough	148 (40)	121 (33)	104 (28)
Headache	58 (16)	58 (16)	58 (16)
Sputum increase	70 (19)	55 (15)	54 (15)
Dyspepsia[c]	22 (7.8)	55 (15)	48 (13)
Respiration abnormalities[c]	22 (5.9)	40 (11)	32 (8.7)

[a] Data are given as No. (%).
[b] Reproduced as the reported pooled safety data from Vertex Pharmaceuticals.[32]
[c] Adverse events that occurred more frequently in patients who received the combination regimens.

Practicing physicians today can use a small but growing number of drugs to treat patients with CF, but some proposed drugs are not readily available. We recommend that any individuals with a diagnosis of CF be considered candidates for genetic testing to determine which *CFTR* mutation underlies their disease. This information can then be used to categorize the mutation into a particular drug class (in classes I through VI) and determine the best therapeutic option to maximize functional improvement.

Author Contributions

Drs Virant-Young, Thomas, and Woiderski, and Ms Powers provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; all authors drafted the article or revised it critically for important intellectual content; all authors gave final approval of the version of the article to be published; and all authors agree 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.

References

1. Cystic Fibrosis Foundation. Patient registry annual data report 2013. https://www.cff.org/2013_CFF_Patient_Registry_Annual_Data_Report.pdf. Accessed July 30, 2015.
2. Narasimhan M, Cohen R. New and investigational treatments in cystic fibrosis. *Ther Adv Respir Dis.* 2011;5(4):275-282.
3. Ramsey B, Davies J, McElvaney N, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med.* 2011;365(18):1663-1672.
4. McCormick J, Green MW, Mehta G, et al. Demographics of the UK cystic fibrosis population: implications for neonatal screening. *Eur J Hum Genet.* 2002;10(10):583-590.
5. Gershman AJ, Mehta AC, Infeld M, Budey MM. Cystic fibrosis in adults: an overview for the internist. *Cleve Clin J Med.* 2006;73(12):1065-1074.
6. Aris RM, Merkel PA, Bachrach LK, et al. Guide to bone health and disease in cystic fibrosis. *J Clin Endocrinol Metab.* 2005;90(3):1888-1896.
7. Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. *N Engl J Med.* 2005;352(19):1992-2001.
8. Wilschanski M, Kerem E. New drugs for cystic fibrosis. *Expert Opin Investig Drugs.* 2011;20(9):1285-1292.

9. Welsh MJ, Smith AE. Molecular mechanisms of CFTR chloride channel dysfunction in cystic fibrosis. *Cell*. 1993;73(7):1251-1254.

10. Pettits R. Cystic fibrosis transmembrane conductance regulator-modifying medications: the future of cystic fibrosis treatment. [published online June 26, 2012] *Ann Pharmacother*. 2012;46(7-8):1065-1074. doi:10.1345/aph1.R076.

11. Lubamba B, Dhooghe B, Noel S, et al. Cystic fibrosis: insight into CFTR pathophysiology and pharmacotherapy. *Clin Biochem*. 2012;45(15):1132-1144.

12. Wilschanski M, Yahav Y, Yaacov Y, et al. Gentamicin-induced correction of CFTR function in patients with cystic fibrosis and *CFTR* stop mutations. *N Engl J Med*. 2003;349(15):1433-1441.

13. Young DC, Zobell JT, Stockmann C, et al. Optimization of anti-pseudomonal antibiotics for cystic fibrosis pulmonary exacerbations. *Pediatr Pulmonol*. 2013;48(11):1047-1061.

14. Howard M, Frizzell RA, Bedwell DM. Aminoglycoside antibiotics restore CFTR function by overcoming premature stop codons. *Nat Med*. 1996;2(4):467-469.

15. Clancy JP, Bebok Z, Ruiz F, et al. Evidence that systemic gentamicin suppresses premature stop mutations in patients with cystic fibrosis. *Am J Respir Crit Care Med*. 2001;163(7):1683-1692.

16. Hermann T. Aminoglycoside antibiotics: old drugs and new therapeutic approaches. *Cell Mol Life Sci*. 2007;64(14):1841-1852.

17. Sermet-Gaudelus I, Renouil M, Fajac A, et al. In vitro prediction of stop-codon suppression by intravenous gentamicin in patients with cystic fibrosis: a pilot study. *BMC Med*. 2007;5:5.

18. Kerem E, Hirawat S, Armoni S, et al. Effectiveness of PTC124 treatment of cystic fibrosis caused by nonsense mutations: a prospective phase II trial. *Lancet*. 2008;372(9640):719-727.

19. Peltz SW, Morsy M, Welch EM, Jacobson A. Ataluren as an agent for therapeutic nonsense suppression. *Annu Rev Med*. 2013;64:28.407-425.

20. Wilschanski M, Miller LL, Shoseyov D, et al. Chronic ataluren (PTC124) treatment of nonsense mutation cystic fibrosis. *Eur Respir J*. 2011;38(1):59-69.

21. Ryan N J. Ataluren: first global approval. *Drugs*. 2014;74(14):1709-1714.

22. Pettit RS, Fellner C. CFTR modulators for the treatment of cystic fibrosis. *PT*. 2014;39(7):500-511.

23. Van Goor F, Hadida S, Grootenhuis PD, et al. Correction of the F508del-CFTR protein processing defect in vitro by the investigational drug VX-809. *Proc Natl Acad Sci U S A*. 2011;180(46):18843-18848.

24. Boyle M, Bell S, Konstan MW, et al. VX-809, an investigational CFTR corrector, in combination with VX-770, an investigational CFTR potentiator, in subjects with CF and homozygous for the F508del-*CFTR* mutation [abstract 212]. *Pediatr Pulmonol*. 2011;S34(suppl):287. doi:10.1002/ppul.21583.

25. Clancy JP, Rowe SM, Accurso FJ, et al. Results of phase IIa study of VX-809, an investigational CFTR corrector compound in subjects with cystic fibrosis homozygous for the F508del-*CFTR* mutation. *Thorax*. 2012;67(1):12-18.

26. Quintana-Gallego E, Delagado-Pecellin I, Acuna CC. CFTR protein repair therapy in cystic fibrosis. *Arch Bronconeumol*. 2014;50(4):146-150.

27. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med*. 2011;365(18):1663-1672.

28. Flume PA, Liou TG, Borowitz DS, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for F508del-*CFTR* mutation. *Chest*. 2012;142(3):718-724.

29. KALYDECO (ivacaftor) Tablets, for oral use [package insert]. Boston, MA: Vertex Pharmaceuticals Inc; 2014. http://www.accessdata.fda.gov/drugsatfda_docs /label/2014/203188s004lbl.pdf. Accessed September 29, 2014.

30. Yu H, Burton B, Huang CJ, et al. Ivacaftor potentiation of multiple CFTR channels with gating mutations. *J Cyst Fibrosis*. 2012;11(3):237-245.

31. Pettit R, Fellner C. CFTR modulators for the treatment of cystic fibrosis. *P T*. 2014;39(7):500-511.

32. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-Ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Eng J Med*. 2015;373:220-231. doi:10.1056/NEJMoa1409547.

33. Two 24-week phase 3 studies of lumacaftor in combination with ivacaftor met primary endpoint with statistically significant improvements in lung function (FEV_1) in people with cystic fibrosis who have two copies of the F508del mutation [press release]. Boston, MA: Business Wire; June 24, 2014. http://investors.vrtx.com/releasedetail.cfm?ReleaseID=856185. Accessed January 11, 2015.

34. Eckford PDW, Ramjeesigh M, Molinski S, et al. VX-809 and related corrector compounds exhibit secondary activity stabilizing active F508del-CFTR after its partial rescue to the cell surface. *Chem Biol*. 2014;21(5):666-678.

35. Donaldson S. Study of VX-661 alone and in combination with ivacaftor in subjects homozygous or heterozygous to the F508del-cystic fibrosis transmembrane conductance regulator (*CFTR*) mutation. ClinicalTrials.gov website. http://clinicaltrials.gov/show/NCT01531673. Accessed May 12, 2014.

36. Moss R. Study of ivacaftor in subjects with cystic fibrosis (CR) who have the R117H-CF transmembrane conductance regulator (*CFTR*) mutation (KONDUCT). ClinicalTrials.gov website. http://clinicaltrials.gov/ct2/show /study/NCT01614457. Accessed May 12, 2014.

37. Vankeerberghen A, Cuppens H, Cassiman JJ. The cystic fibrosis transmembrane conductance regulator: an intiriguing protein with pleiotropic functions. *J Cyst Fibros*. 2002;1(1):13-29.