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Is Triple Combination CFTR Modulator Therapy Effective in Improving the Quality of Life of Patients with Cystic Fibrosis Who Have One Phe508del Allele?

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Is triple combination CFTR modulator therapy effective in improving the quality of life of patients with cystic fibrosis who have one Phe508del allele?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not "Is triple combination CFTR modulator therapy effective in improving the quality of life of patients with cystic fibrosis who have one Phe508del allele?"

Study Design: A systematic review of three, double-blind, randomized controlled trials (RCTs) published in 2018 and 2019.

Data Sources: All RCTs were found using PubMed. All articles were published in peer-reviewed journals and selected based on credibility, relevance to the clinical question, date of publication, population, and evaluation of patient-oriented evidence that matters (POEMs).

Outcome measured: All three studies utilized the CFQ-R respiratory domain score, a 50-item questionnaire that assesses the impact of cystic fibrosis on health-related quality of life (HRQoL). Scores range from 0 – 100 with higher scores indicating a higher patient-reported HRQoL with respect to respiratory status. 4 points is considered a minimal clinical importance. The absolute change from baseline CFQ-R scores were determined at the end of each intervention period.

Results: Clinically significant improvements in CFQ-R scores from baseline were revealed in all three studies. CFQ-R scores increased 17.1 points in the Davies et al. study (*N Engl J Med*. 2018;379(17):1599-1611. doi: 10.1056/NEJMoa1807119 [doi]), 24.4 points in the Keating et al. study (*N Engl J Med*. 2018;379(17):1612-1620. doi: 10.1056/NEJMoa1807120 [doi]), and 17.5 points in the Middleton et al study (*N Engl J Med*. 2019;381(19):1809-1819. doi:10.1056/nejmoa1908639). However, the Davies et al. study revealed clinically significant improvements in CFQ-R scores in both the intervention and placebo group rendering these results inconclusive. The Middleton et al. study provided statistically significant results and a mean treatment difference of 20.2 points with a statistically significant p-value (<0.001).

Conclusion: Triple combination CFTR modulator therapy demonstrated clinically significant improvements in CFQ-R scores from baseline in patients with cystic fibrosis who have one Phe508del allele, indicating an improvement in quality of life. However, the evidence is inconclusive as one of the studies revealed clinically significant improvements in both the intervention and placebo group. Further research is needed to demonstrate the potential of this therapy using larger intervention groups and longer treatment periods in order to assess for statistically significant findings.

Key Words: "Cystic Fibrosis" "CFTR modulator therapy"

INTRODUCTION

Cystic Fibrosis (CF) is a progressive, multi-organ, hereditary disease that impairs lung and digestive function. This disease follows an autosomal recessive inheritance pattern and is caused by mutations in the CFTR gene.[1] The CFTR gene encodes for CFTR protein, an ion channel that regulates the transport of chloride and other ions at the surface of cells. This protein is located on every organ in the body that produces mucus, including the lungs, liver, pancreas, intestines, and sweat glands. CFTR protein in patients with CF, however, either functions improperly or is never created. This causes a build up of abnormally thick, sticky mucus in various organs that clog the airways of the lungs and pancreatic and bile ducts. An array of symptoms manifest as a result, including a persistent cough with mucus, frequent lung infections, wheezing, shortness of breath, chronic nasal congestion, sinus infections, sleep disturbances and poor growth or weight gain. These manifestations ultimately result in a decreased quality of life and decreased life-span.[2]

Approximately 70,000 people worldwide are living with CF, and it is estimated that 1,000 new cases are diagnosed each year.[2] In 2017, there were 129,542 clinic visits and 22,535 hospitalizations.[3] Managing CF is complex and requires medical professionals trained in the field of this disease. Although there is no cure for CF, medications are used to ease symptoms and reduce potential complications. There are several medical interventions required for CF patients which are tailored to each patient depending upon their symptoms and state of health. These options may include antibiotics, steroids, antihistamines, mucolytics, bronchodilators, and oral pancreatic enzymes. In addition to medical therapy, chest physical therapy termed “vest therapy” and pulmonary rehab are initiated to help improve lung function. This translates to a mean

annual health care cost of $15,571;[5] however, this cost has since increased with the FDA approval of CFTR modulator therapy in 2012.

For those with CF who have certain genetic mutations, CFTR modulator therapy is available. This therapy represents a class of medications that address the genetic defect of CF. The Phe508del mutation is the most common mutation in the CFTR gene, and 90% of CF patients carry this on at least one allele.[7] Phe508del causes a defect in the intracellular processing and trafficking of the CFTR protein, which drastically reduces the quantity of the CFTR protein at epithelial cell surfaces and creates defective channel gating that further limits anion transport. CFTR modulator therapy restores the function of CFTR protein by increasing the amount delivered to the surface of cells while increasing its channel-gating activity.[6] Ivacaftor (Kalydeco), lumbacaftor-ivacaftor (Orkambi), and tezacaftor-ivacaftor (Symdeko) are CFTR modulators that are currently available. In order to qualify for treatment, however, patients must have two Phe508del alleles or a residual function mutation, a mutation that is responsive to CFTR modulator therapy.[7]

Among patients who have at least one Phe508del allele, one third have a minimal-function (MF) CFTR as the second allele. The MF allele has been shown to be unresponsive to CFTR modulators, and thus, the above CFTR modulators have not been approved for this population of CF patients.[8] Two next-generation CFTR modulators, VX-659 and VX-445, each in triple combination with tezacaftor-ivacaftor (TEZ-IVA) are being researched as adjunctive therapy for CF patients with one Phe508del allele regardless of the second allele. On October 21, 2019, the FDA approved Trikafta (elexacaftor(VX-445)-TEZ-IVA), the first triple combination therapy.[9] This breakthrough therapy is available for 90% of patients with CF, including those with one Phe508del allele who previously had no options for CFTR modulator therapy. This

gives 30% of patients who did not previously qualify for CFTR modulator therapy a chance to correct the underlying defect of CF, restore high levels of functioning CFTR protein, and improve their daily symptoms. This paper evaluates three RCTs and compares the efficacy of triple combination CFTR modulator therapy as an adjunctive therapy for helping improve symptoms and the quality of life of patients with CF who have one Phe508del allele.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Is triple combination CFTR modulator therapy effective in improving the quality of life of patients with cystic fibrosis who have one Phe508del allele?"

METHODS

Studies were selected if they met the criteria based on populations, interventions, comparisons, and outcomes measured. It was necessary that all studies targeted patients who are clinically diagnosed with CF and specifically have one Phe508del allele (Phe508del-MF genotypes). Studies were also selected based on their credibility, relevance to my clinical question, and inclusion of patient-oriented outcomes. These studies were found using searches from PubMed and NCBI with keywords "Cystic Fibrosis" and "CFTR modulator therapy". Articles were considered credible if they contained double-blind randomization and published in peer reviewed journals. All articles were in the English language and published in peer-reviewed journals. Inclusion criteria for this review was randomized controlled trials (RCTs) published after 2008 and Phe508del-MF genotypes. Studies were excluded if they were published before 2008, did not include Phe508del-MF genotypes, and did not include patient-oriented outcomes. Statistical analyses used in these studies include the absolute change from baseline CFQ-R scores with adjustment for baseline scores, confidence intervals, and p-values.

The intervention in each study comprised of a triple combination CFTR modulator therapy regimen and compared it to a matched triple placebo. Keating et al. and Middleton et al. used VX-445, also referred to as elexacaftor, in triple combination with TEZ-IVA as the triple combination CFTR modulator therapy, while Davies et al. used VX-659 in triple combination with TEZ-IVA. Both elexacaftor (VX-445) and VX-659 have the same mechanism of action in that they both improve Phe508del CFTR protein processing and trafficking while enhancing its function. Outcomes were measured by the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain scores and their absolute change from baseline were determined.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Davies[8] (2018)	RCT	30	≥ 18 yrs of age	CF pts, ≥ 18 years of age, heterozygous for Phe508del and a minimal function mutation (Phe508del-MF genotypes), FEV_1 of 40 – 90%, stable disease, sweat chloride concentration of ≥ 60 mmol/L, weight ≥ 35 kg.	Lung infection with organisms associated with a more rapid decline in pulmonary status; risk factors for Torsade de Pointes; G6PD deficiency; history of any comorbidity that might confound study results or pose additional risks, cirrhosis, hemolysis, solid organ or hematological transplantation, or peptic ulcer; GERD, gastritis, gastric lesions; history or evidence of cataract or lens opacity; clinically significant laboratory abnormalities at screening, acute upper or lower respiratory infection or pulmonary exacerbation within 28 days before the first dose of study drug; use of a CFTR modulator within 14 days before screening, pregnant or breastfeeding women.	1	240 mg of VX-659 one daily in triple combination with tezacaftor (100 mg 1x/day) and ivacaftor (150 mg every 12 hours) vs triple placebo.
Keating[10] (2018)	RCT	33	≥ 18 yrs of age	CF pts, ≥ 18 years of age, heterozygous for Phe508del and a minimal function mutation (Phe508del-MF genotypes), FEV_1 of 40 – 90%, stable disease, sweat chloride concentration of ≥ 60 mmol/L, weight ≥ 35 kg.	Same as above plus the following: history of alcohol or drug abuse; acute illness not related to cystic fibrosis within 14 days before first dose of study drug; prior participation in a study of an investigational treatment other than a CFTR modulator within 28 days.	0	200 mg VX-445 once daily in triple combination with tezacaftor (100 mg 1x/d) and ivacaftor (150 mg every 12 hrs) vs triple placebo.
Middleton[11] (2019)	RCT	403	≥ 12 yrs of age	CF pts, ≥ 12 years of age, Phe508del-MF genotypes, FEV1 of 40 to 90%, stable lung disease, sweat chloride concentration of at least 60 mmol per liter.	Same as above plus the following: history of alcohol or drug abuse; acute illness not related to cystic fibrosis within 14 days before first dose of study drug; prior participation in a study of an investigational treatment other than a CFTR modulator within 28 days.	2	200 mg of elexacaftor once daily in triple combination with tezacaftor (100 mg 1x/d) and ivacaftor (150 mg q 12 hrs) vs matched placebo.

OUTCOMES

The outcome measured in this review is the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score, a patient reported outcome that measures health-related quality of life (HRQoL) in respect to respiratory status. There are 50 questions about gastrointestinal and respiratory symptom difficulties, limitations in activities of daily life, number of medications and duration of treatments each day, psychosocial impediments, and emotional distress. Scores range from 0 – 100, and higher scores indicate a higher patient-reported HRQoL with respect to respiratory status. 4 points is considered a minimal clinical important difference. The absolute change from baseline score at the start of the therapy was adjusted for baseline scores and determined at the end of the intervention period.

RESULTS

All three studies in this review enrolled CF patients with Phe508del-MF genotypes and evaluated the safety and efficacy of triple combination CFTR modulator therapy. Davies et al. conducted a three-part, randomized, parallel-track, placebo or active-controlled, double-blind, multicenter, dose-ranging, phase 2 trial. A phase 1 trial was performed prior to evaluate pharmacokinetics and initial safety of VX-659-tezacaftor-ivacaftor. This trial enrolled patients 18 years of age or older with mild to moderate stable CF and with Phe508del-Phe508del and Phe508del-MF genotypes; however, this review focuses on Phe508del-MF genotypes. Additional inclusion and exclusion criteria can be referenced in table 1. In phase 2, 63 patients with Phe508del-MF genotypes were enrolled and underwent randomization. A randomization ratio of 1:2:2:1 was used to decrease variability and increase accuracy. Patients with Phe508del-MF genotypes were assigned to receive 4 weeks of active treatment with oral VX-659 at doses 80, 240, or 400 mg once daily in triple combination with tezacaftor (100 mg once daily) and

ivacaftor (150 mg every 12 hours) or to receive oral triple placebo. This review focused on using the placebo as the control group and 240 mg of oral VX-659 as the intervention group. A total of 20 patients were assigned to receive 240 mg of VX-659 in combination with TEZ-IVA while 10 patients were assigned to receive the oral triple placebo. Adverse events ranged from mild to severe. None lead to discontinuation of the trial regimen.[8]

The trial groups in Davies et al. were well balanced across intervention groups regarding at baseline age, sex, percentage of predicted FEV1, and sweat chloride concentrations. Baseline CFQ-R scores were determined and revealed that the mean baseline CFQ-R respiratory domain score was numerically higher in the placebo group than in the active-treatment group. Consequently, analysis of the change in the CFQ-R respiratory domain score was performed both with and without adjustment for the baseline score. Assessments for efficacy and improvement in the CFQ-R respiratory domain score were observed on day 29 of treatment.[8,10] The absolute change from baseline CFQ-R with adjustment for the baseline scores at day 29 was 17.1 +/- 2.6 (95% CI 11.9 – 22.2) in the intervention group compared to 13.1 +/- 3.6 (95% CI, 5.9 – 20.3) in the placebo group. The authors of this study state that a minimal clinical important difference in CFQ-R scores is 4 points; thus, this study revealed clinically significant improvements in CFQ-R scores from baseline. However, both the intervention group and placebo group experienced significant improvements in CFQ-R scores. These results are summarized in Table 2 below and include the 95% confidence intervals.[8,10]

Keating et al. conducted a trial with similar design and conduct to those presented in the companion trial of VX-659. Similarly, this was a three-part, randomized, parallel-track, placebo or active-controlled, double-blind, multicenter, dose-ranging, phase 2 trial. This trial enrolled patients 18 years of age or older with mild to moderate stable CF and with Phe508del-Phe508del

and Phe508del-MF genotypes. 65 patients with Phe508del-MF genotypes were enrolled and underwent randomization similar to that of the previous study. Patients with Phe508del-MF genotypes were randomly assigned to receive 4 weeks of active treatment with VX-445 at a dose of 50, 100, 200 mg orally once daily in triple combination with tezacaftor (100 mg daily) and ivacaftor (150 mg every 12 hours). This review focused on using the placebo as the control group and 200 mg of oral VX-445 as the intervention group. A total of 21 patients were assigned to receive 200 mg of VX-445 in combination with TEZ-IVA while 12 patients were assigned to receive the oral triple placebo. Adverse events ranged from mild to severe. None lead to discontinuation of the trial regimen.[10]

The trial groups in Keating et al. were well balanced across intervention groups regarding at baseline age, sex, percentage of predicted FEV1, and sweat chloride concentrations. Comparable to the Davies et al. study, an analysis of the change in the CFQ-R respiratory domain score was performed with adjustment for the baseline score. Assessments for efficacy and improvement in the CFQ-R respiratory domain score (CFQ-R scores) were observed on day 29 of treatment.[8,10] The absolute change from baseline scores with adjustment for baseline scores at day 29 was 24.4 +/- 3.3 (95% CI 17.8 – 31.0) in the intervention group compared to 3.1 +/- 4.4 (95% CI, -5.6 – 11.8) in the placebo group. The authors of this study state that a minimal clinical important difference in CFQ-R scores is 4 points; thus, this study revealed clinically significant improvements in CFQ-R scores from baseline. These results are summarized in Table 2 below and include the 95% confidence intervals.[8,10]

Middleton et al. conducted a phase 3, multicenter, randomized, double-blind, placebo controlled trial to confirm the safety and efficacy of elexacaftor(VX-445)-tezacaftor-ivacaftor in patients 12 years of age or older with mild to moderate stable CF and Phe508del-MF genotypes.

403 patients were randomly assigned in a 1:1 ratio, and 200 received elexacaftor (200 mg once daily) in triple combination with tezacaftor (100 mg once daily) and ivacaftor (150 mg every 12 hours) while 203 patients received a matched triple placebo. Serious adverse events occurred in 28 patients (13.9%) in the intervention group versus 42 patients (20.9%) in the placebo group. Two patients receiving elexacaftor-TEZ-IVA discontinued the trial regimen because of adverse events; 1 patient experienced a rash while the other developed portal hypertension.[11]

The trial groups in Middleton et al. were well matched at baseline, including sex, age, geographic region, percentage of predicted FEV1, BMI, sweat chloride concentration, and CFQ-R scores. The absolute change in CFQ-R scores were analyzed from baseline through week 24 for efficacy and improvements. Those receiving the triple combination CFTR therapy had an absolute change from baseline CFQ-R score of 17.5 (95% CI, 15.6 – 19.5) compared to the placebo group of -2.7 (95% CI, -4.6 to -0.8). CFQ-R scores were interpreted similar to that of the previous two studies, and therefore, clinically significant improvements in CFQ-R scores were demonstrated in the intervention group. A mean treatment difference was provided in this study and was 20.2 points relative to placebo. A p-value <0.001 was provided for all values mentioned, indicating these results to be statistically significant.[11] Mean treatment differences were not provided in the Davies et al. or Keating et al. studies; however these values can be inferred and are 4 points and 21.3 points respectively.[8,10]

Table 2. Absolute Change From Baseline of CFQ-R Respiratory Domain Score Adjusted for Baseline Scores and Mean Treatment Differences

	Intervention Group	Triple Placebo Group	Mean Treatment Difference
Davies et al. 95% CI	17.1 +/- 2.6 (11.9 – 22.2)	13.1 +/- 3.6 (5.9 – 20.3)	4
Keating et al. 95% CI	24.4 +/- 3.3 (17.8 – 31.0)	3.1 +/- 4.4 (-5.6 – 11.8)	21.3
Middleton et al. 95% CI P Value	17.5 (15.6 – 19.5) <0.001	-2.7 (-4.6 – -0.8) <0.001	20.2 (17.5 – 23.0) <0.001

DISCUSSION

Since the isolation of the CFTR gene in 1989, significant progress has been made in understanding its role.[2] The CFTR gene has become a target for medical therapies, which has allowed the development of significant medical advances namely CFTR modulator therapy. A triple combination CFTR modulator therapy, Trikafta (elexacaftor-ivacaftor-tezacaftor), was newly approved in October 2019 for CF patients 12 years and older with at least one Phe508del allele. The cost of Trikafta is $311,503 annually, and it is expected that policies will vary among insurance providers in terms of coverage. Given this drug was recently approved, it may take up to 6 months for insurance companies to formally review the drug and add it to their list of covered drugs. It is predicted that most insurance companies will provide coverage; however, patients will need to pay out of pocket if their insurance does not choose to cover it.

This review evaluated the efficacy of triple combination CRTR modulatory therapy as an adjunctive treatment for CF patients with Phe508del allele to improve health-related quality of life. All three studies found clinically significant differences in CFQ-R scores after intervention with triple combination CFTR modulator therapy. CFQ-R scores in all three studies increased 4 points or more, suggesting this therapy to be to be effective in improving health-related quality of life of CF patients with one Phe508del allele. CFQ-R scores increased 17.1 points in the Davies et al. study, 24.4 points in the Keating et al. study, and 17.5 points in the Middleton et al. study. However, Davies et al. revealed improvements in both the intervention group (17.1 points) and placebo group (13.1 points), rendering these results inconclusive. Middleton et al. provided statistically significant p-values for all results and a mean treatment difference of 20.2 points with a statistically significant p-value. The results from this study support the efficacy of this therapy and indicate a subject improvement in quality of life.

All three studies had limitations based on validity, sample size, length of study, and study population. The confidence intervals in all three studies are wide, which makes the results less precise and brings into question validity. Davies et al. and Keating et al. used small sample sizes within their studies, and this affects the validity and reliability of these results. Additionally, the randomization allocation was not concealed from those enrolling subjects in any three studies which introduces a selection bias. Lastly, Davies et al. and Middleton et al. did not perform worst case analyses for missing outcome data from subjects lost during their respective trial periods. This factor also introduces bias within these studies and make them less valid.

Long-term efficacy and tolerance of triple combination CFTR modulator therapy is not demonstrated within the Davies et al. and Keating et al. studies as the intervention periods each lasted 4 weeks in length. Another limitation of the studies is the age of patients enrolled. Davies et al. and Keating et al. trialed patients 18 years of age or older, while Middleton et al trialed patients 12 years of age or older. Thus, treatment effects were not demonstrated in younger populations of CF patients. Most children with CF are diagnosed by age 2 and exhibit respiratory symptoms through childhood years.[2] Younger CF patients could benefit from CFTR modulator therapy; however, the efficacy and safety of this therapy in a younger patient population has not been demonstrated. Moreover, patients with CF who had comorbidities, a pulmonary exacerbation within the past 28 days, or a recent lung infection were excluded from these studies. Patients with CF often have multi-organ manifestations and at least 1 pulmonary exacerbation per year that requires on average 29 days of treatment.[12] The safety and efficacy was not evaluated for patients who fall into these categories, and this is nonetheless a reality for CF patients.

CONCLUSION

Although this systematic review is limited as it only evaluates results from early trials of triple combination CFTR modulator therapy research, the results are promising. Triple combination CFTR modulator therapy provided clinically significant improvements in CFQ-R scores from baseline in patients with CF who have one Phe508del allele, supporting its efficacy and indicating a subjective improvement in quality of life; however, the evidence is inconclusive as the Davies et al. study revealed improvements in both the intervention and placebo groups. There was a mean treatment difference of 4 points relative to placebo in the Davies et al. study, but it is unknown if this value is statistically significant as no p-value is provided for this result. The studies by Keating et al. and Middleton et al. had larger mean treatment differences in comparison, and Middleton et al. indicated this value to be a statistically significant difference ($P < 0.001$). Overall, CFQ-R respiratory domain scores improved with triple combination CFTR modulator therapy to a larger degree in comparison to placebo. The chance for even a small improvement in quality of life in respect to respiratory function for CF patients with one Phe508del allele is of potential benefit.

In order to further demonstrate the potential this treatment has to treating the underlying protein defect, additional trials should be performed with larger intervention groups and longer intervention periods. Future studies should include worst case analyses and achieve randomization allocation concealment to prevent bias and improve validity. In addition, studies should be expanded to involve CF patients younger than 12 years old. This therapy has the potential to prevent multi-organ manifestations of this disease and may allow young children with CF to have a normal life expectancy, so starting this therapy at an earlier stage of disease would be of tremendous benefit. There is currently a trial of Trikafta underway in children with

CF ages 6 to 11, and the results are to be expected in 2020. The CF Foundation is also funding a lab research to test whether people with other rare mutations, an estimated 10% of the CF patient population, may benefit from Trikafta.[13] Trikafta is predicted to eventually cut the amount of medications taken daily in half and reduce the amount time spent each day performing therapies.[13] This would significantly reduce daily treatment time, overall cost, and treatment burden placed on those with living with CF. Perhaps future trials may be able to demonstrate this concept.

REFERENCES

1. NIH. U.S. National Library of Medicine. Cystic fibrosis - Genetics Home Reference. https://ghr.nlm.nih.gov/condition/cystic-fibrosis#genes. Published October 1, 2019. Accessed October 6, 2019.
2. CF Foundation. About Cystic Fibrosis. CF Foundation. https://www.cff.org/what-is-cf/about-cystic-fibrosis/. Accessed October 6, 2019.
3. Cystic Fibrosis Foundation. 2017 Cystic Fibrosis Foundation Patient Registry Highlights. https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Cystic-Fibrosis-Foundation-Patient-Registry-Highlights.pdf. Published 2017. Accessed October 6, 2019.
4. Mayo Clinic. Cystic fibrosis. https://www.mayoclinic.org/diseases-conditions/cystic-fibrosis/diagnosis-treatment/drc-20353706. Published July 9, 2019. Accessed October 7, 2019.
5. Gool KV, Norman R, Delatycki MB, Hall J, Massie J. Understanding the costs of care for cystic fibrosis: An Analysis by Age and Health State. *Value in Health*. 2013;16(2):345-355. doi:10.1016/j.jval.2012.12.003.
6. Ong T, Ramsey BW. New Therapeutic Approaches to modulate and correct cystic fibrosis transmembrane conductance regulator. *Pediatr Clin North Am*. 2016;63(4):751–764. doi:10.1016/j.pcl.2016.04.006
7. CF Foundation. CFTR Modulator Therapies. https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Medications/CFTR-Modulator-Therapies/. Accessed December 6, 2019.
8. Davies JC, Moskowitz SM, Brown C, et al. VX-659-tezacaftor-ivacaftor in patients with cystic fibrosis and one or two Phe508del alleles. *N Engl J Med*. 2018;379(17):1599-1611. doi: 10.1056/NEJMoa1807119 [doi].
9. U.S. Food and Drug Administration. FDA approves new breakthrough therapy for cystic fibrosis.. https://www.fda.gov/news-events/press-announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis. Published October 21, 2019. Accessed December 6, 2019.
10. Keating D, Marigowda G, Burr L, et al. VX-445-tezacaftor-ivacaftor in patients with cystic fibrosis and one or two Phe508del alleles. *N Engl J Med*. 2018;379(17):1612-1620. doi: 10.1056/NEJMoa1807120 [doi].
11. Middleton PG, Mall MA, Dřevínek P, et al. Elexacaftor–Tezacaftor–Ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med*. 2019;381(19):1809-1819. doi:10.1056/nejmoa1908639.
12. Cystic Fibrosis Foundation. 2017 Patient Registry Annual Data Report. https://www.cff.org/Research/Researcher-Resources/Patient-Registry/2017-Patient-Registry-Annual-Data-Report. Published 2018. Accessed November 23, 2019.
13. CF Foundation. Trikafta™ Approval: Community Frequently Asked Questions. https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Trikafta-Approval-Community-FAQ/. Published October 25, 2019. Accessed December 6, 2019.