EDITORIAL

CFTR Modulator Therapy for Cystic Fibrosis

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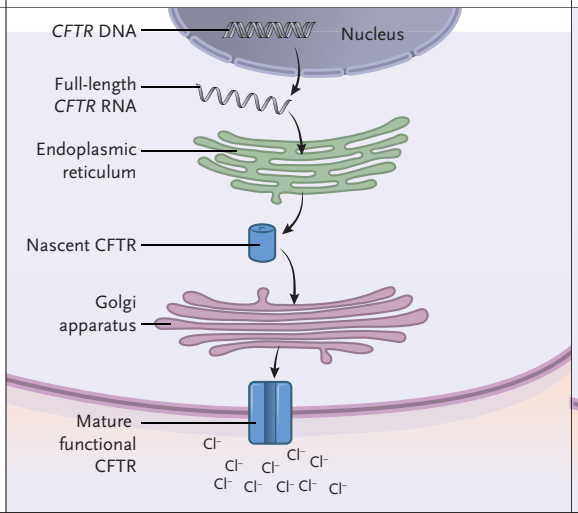
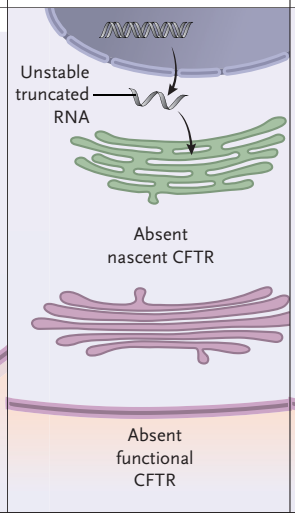
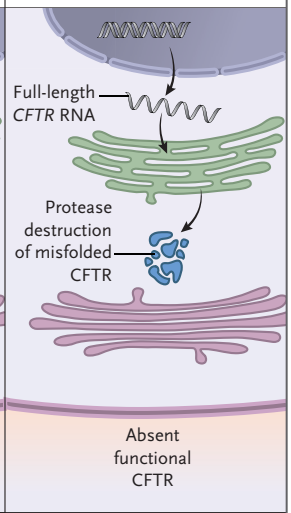
Cystic fibrosis is a disease of abnormal ion transport through epithelium that results in progressive lung disease as well as the involvement of other organs including the pancreas, gut, and liver. Cystic fibrosis is caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (*CFTR*), and inheritance is autosomal recessive, meaning that people with cystic fibrosis carry two *CFTR* mutations, one on each allele. In general, *CFTR* mutations cause reduced quantity or function of CFTR protein at the cell surface, but the specific mechanisms leading to CFTR deficiency are quite distinct among different classes of mutations (Fig. 1). For instance, Phe508del, a class II mutation and by far the most common cystic fibrosis–causing mutation, results in minimal or no functional expression of CFTR, whereas other mutations allow for residual CFTR function (class IV to VI). Residual-function mutations are often associated with milder disease.

CFTR modulator therapies are being developed to treat cystic fibrosis at the origin of the disease. Potentiators such as ivacaftor increase the channel gating of CFTR to enhance chloride ion transport, and ivacaftor therapy improves pulmonary function and increases weight in patients with gating mutations such as Gly551Asp (class III).[1] Despite these positive effects, patients who receive ivacaftor still need other treatments to control the disease, including pancreatic-enzyme replacement, inhaled mucolytic drugs, and antibiotic therapies. In addition, such gating mutations are rare (affecting approximately 5% of patients with cystic fibrosis), whereas patients who are homozygous for the Phe508del mutation represent 40 to 50% of the population with cystic fibrosis in Europe and North America. Ivacaftor is ineffective in persons with two Phe508del mutations.[2]

In contrast to potentiators, CFTR correctors work by improving intracellular trafficking of CFTR protein to the cell surface. Although this mechanism results in CFTR expression, monotherapy with correctors such as lumacaftor is also ineffective in patients with two Phe508del mutations,[3] because the Phe508del protein is not functioning properly. However, Phe508del CFTR once expressed at the cell surface responds to potentiators; therefore, combination therapy has been explored. The first such combination of CFTR modulators that was approved for people with cystic fibrosis who are homozygous for the *CFTR* Phe508del mutation was lumacaftor–ivacaftor (Orkambi).[4] Although this medication was shown to be effective in clinical trials, the overall efficacy was modest and less than that of ivacaftor in patients with Gly551Asp, a finding that is possibly related to drug–drug interaction between lumacaftor and ivacaftor.[5] Concerns were also raised about the side effects of lumacaftor–ivacaftor, including (transient) dyspnea, liver damage, and potential interactions of lumacaftor with other drugs.

Two clinical trials now reported in the *Journal* examine tezacaftor, a new corrector agent, given in combination with ivacaftor. Taylor-Cousar and colleagues[6] report improved pulmonary function after tezacaftor–ivacaftor therapy given to patients 12 years of age or older who had cystic fibrosis and were homozygous for the Phe508del mutation. The primary end point of the trial was the absolute change in the percentage of predicted forced expiratory volume in 1 second (FEV_1) from baseline through week 24. FEV_1, a measure of pulmonary function, increased by 3.4 percentage points in the tezacaftor–ivacaftor group and decreased by 0.6 percentage points in the placebo group; thus, the treatment effect was 4.0 percentage

Class	Normal	I	II
CFTR defect	—	No functional CFTR protein	CFTR trafficking defect
Type of mutation	—	Nonsense Frameshift Canonical splice	Missense Amino acid deletion
Specific mutation examples	—	Gly542X Trp1282X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr
Mechanism			

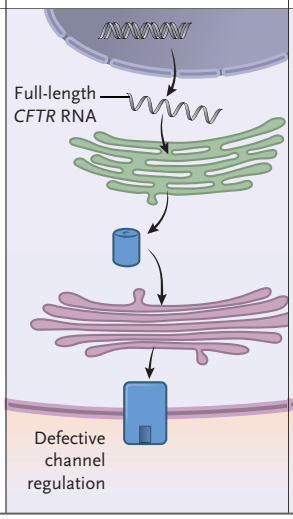
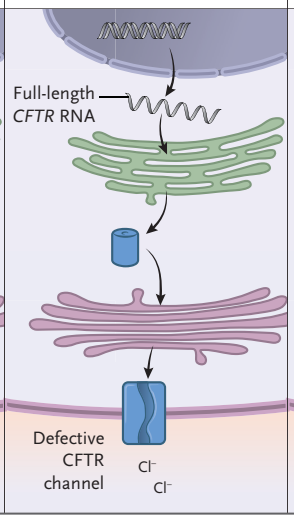
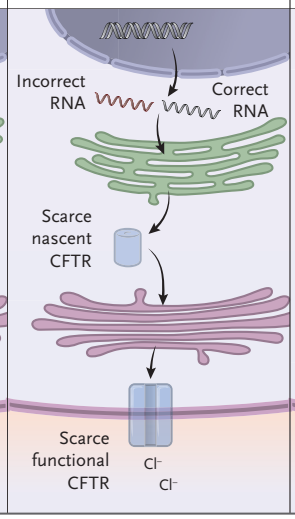
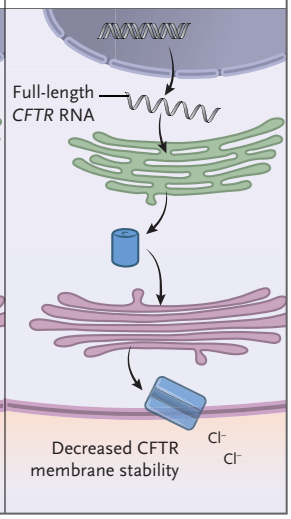
Class	III	IV	V	VI
CFTR defect	Defective channel regulation	Decreased channel conductance	Reduced synthesis of CFTR	Decreased CFTR stability
Type of mutation	Missense Amino acid change	Missense Amino acid change	Splicing defect Missense	Missense Amino acid change
Specific mutation examples	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA
Mechanism				

Figure 1 (facing page). Classes of Mutations in the Gene Encoding Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*).

Depending on the molecular defect, *CFTR* mutations can result in no functional CFTR protein expression because of premature stop codons, frameshifts for deletions or insertions (class I), or a CFTR trafficking defect caused by intracellular degradation of misfolded protein (class II). Other mutations can result in CFTR protein expression but defective channel regulation or gating (class III), reduced chloride conductance (class IV), reduced synthesis (class V), or decreased stability of CFTR (class VI).

points. As in other trials of CFTR modulators, the improvement in pulmonary function was seen early after initiation and persisted throughout the trial period. In addition to the increase in FEV_1, the annual pulmonary exacerbation rate was lower by 35% with tezacaftor–ivacaftor than with placebo, and the quality of life was improved. Treatment did not result in increased respiratory symptoms or a decline in postdose FEV_1 or in abnormal liver-function tests, results that were different from the experience with lumacaftor–ivacaftor therapy.

The article by Rowe and colleagues[7] summarizes a crossover study of ivacaftor monotherapy, tezacaftor–ivacaftor combination therapy, or placebo given for 8 weeks to patients with cystic fibrosis who were heterozygous for the Phe508del mutation and a second allele mutation associated with residual CFTR function. With respect to FEV_1, the treatment effect versus placebo from the baseline value to the average of the week 4 and week 8 measurements was 4.7 percentage points for ivacaftor alone and 6.8 percentage points for tezacaftor–ivacaftor. Again, treatment effects on FEV_1 were seen early and persisted throughout the trial. Both active treatments resulted in a significantly better quality of life than did placebo.

In summary, tezacaftor–ivacaftor combination therapy improves lung function (as assessed by FEV_1) in patients with cystic fibrosis who have the most common genotype, an effect similar to that of lumacaftor–ivacaftor but with a better side-effect profile. The combination also improves lung function in patients with a residual-function mutation, to a similar degree as ivacaftor monotherapy. Whether the combination of increased FEV_1 and reduced exacerbation rate will result in greater treatment effects over time is unclear although conceivable, because exacerbations contribute to a more rapid decline in pulmonary function. Results from the open-label extension studies in which the majority of the trial participants were enrolled may help clarify this in the near future.

Nevertheless, the trials show that although CFTR modulator therapies have measurable beneficial effects on some aspects of the disease, there is still an unmet need for truly effective new therapies to be developed for all persons with cystic fibrosis. The clinical efficacy of the current combination therapies for patients with cystic fibrosis who have the most common CFTR genotype (Phe508del/Phe508del) is suboptimal and falls within the range of established symptomatic therapies, such as nebulized inhaled hypertonic saline or recombinant human DNAse. Whether new combination drugs that are in the drug-development pipeline[8] will ultimately result in a clinically meaningful improvement in lung function and clinical status needs to be evaluated.

Although preliminary results of triple combination therapy in patients with the Phe508del mutation look very promising,[9] other approaches need to be explored as well. These should include *CFTR* gene replacement with new delivery strategies that result in effective and long-lasting expression of CFTR in airway epithelium, gene editing with tools such as CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats associated with Cas9 nuclease), or induced pluripotent stem-cell therapy. Because any approach aiming to increase CFTR ion transport may still not sufficiently address all aspects of the disease, other therapies need to be advanced as well — for instance, in the areas of nutrition and digestion, mucociliary clearance, and the development of new antimicrobials.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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