VIEWPOINT

Cystic Fibrosis: Breakthrough Drugs at Break-the-Bank Prices

囊性纤维化：突破性药物，价格高昂

Fibrosis quística: Medicamentos de última generación a precios sin competencia

David M. Orenstein, MD, MA, *United States*; Brian P. O'Sullivan, MD, *United States*; Paul M. Quinton, PhD, *United States*

Author Affiliations
Antonio J. and Janet Palumbo Cystic Fibrosis Center, Children's Hospital of Pittsburgh of UPMC, and University of Pittsburgh, Pennsylvania (Dr Orenstein); Geisel School of Medicine at Dartmouth (Dr O'Sullivan), Hanover, New Hampshire; University of California San Diego School of Medicine, University of California Riverside School of Medicine, and Rady Children's Hospital, California (Dr Quinton).

Correspondence
David M. Orenstein, MD, MA
davido@pitt.edu

Citation
Global Adv Health Med. 2015;4(6):8-9;57. DOI: 10.7453/gahmj.2015.123

Key Words
Pharmaceuticals, costs, cystic fibrosis

Progress in cystic fibrosis (CF) over the past few decades has been nothing short of miraculous on several fronts: median survival in the United States has increased from 15 years in 1975 to 41 years in 2013, with predictions into the 50s for children born this century.[1] Our understanding of the genetic and cellular underpinnings of CF have similarly grown exponentially, beginning in the 1980s with the identification of the cellular ion transport defect[2] and the discovery of the gene, dubbed CFTR (cystic fibrosis transmembrane conductance regulator).[3] Now in the past 3 years, with the advent of mutation-specific therapies, we have entered a new era that promises even greater improvement in the quality and the length of lives.

The first of these small molecule therapies to come to fruition (and to market) was Vertex Pharmaceuticals' (Boston, Massachusetts) ivacaftor (sold as Kalydeco), which received FDA approval in 2012. In a clinical trial, ivacaftor brought about dramatic improvements in pulmonary function and body weight as well as crucial confirmation of a CFTR cellular effect, reduced elevated sweat chloride concentrations—for centuries the hallmark of the disease—to near normal levels.[4] That's the good news. The bad news is that (1) this compound is effective for only a few patients with CF, specifically those (less than 10%) whose CFTR gene mutations translate into a defective protein that is transported successfully through the cytoplasm to insert into the plasma (cell) membrane but fails to gate (open for; ie, conduct) chloride and bicarbonate normally and (2) the drug is phenomenally expensive ($311 000/y wholesale from Vertex, $376 000/y through a specialty pharmacy). And very recently, another drug, actually a combination of ivacaftor and another compound known as lumacaftor, appears to have a statistically significant but limited effect for many of the remaining patients, specifically those who are homozygous for the F508del mutation, ie, some 50% of all US patients. In this mutation, the CFTR protein starts to be made in the cytoplasm, but very little survives the journey from the cytoplasm (endoplasmic reticulum) to the plasma (cell) membrane, and the small amount that does complete the trip still functions only very poorly; thus defective proteins from this mutation need help to get to their destination in the cell membrane. Lumacaftor provides the ride, but then the protein still needs help to open properly and ivacaftor provides the slide. This combination drug was approved by the US Food and Drug Administration (FDA) this year and is marketed as Orkambi, also made by Vertex. In Phase 3 trials, the combination appeared to lengthen significantly the time between pulmonary infections that require intravenous antibiotic treatment and to improve pulmonary function.[5] That's the good news. However, the magnitude of the pulmonary function improvement, at some 3%, is much smaller than that seen with ivacaftor alone in patients with the G551D mutation (the most common of the gating mutations) and, although statistically significant, is of marginal clinical benefit. Further, there is some evidence that the 2 components of the combination drug do not work well together, with 1 interfering with the function of the other.[6] Despite these limitations, but perhaps predictably, the price of the drug is an astounding $259 000 per year from Vertex, and either $286 892.40 from one of the specialty pharmacies that supply the drug to patients, or, if one is willing to do aggressive comparison shopping, it can be purchased for $286 890.24 per year from another specialty pharmacy, for an annual savings of $2.16! It is surely intriguing that the combination of ivacaftor and lumacaftor—Orkambi—is actually about $50 000 per year cheaper than ivacaftor alone and even more intriguing since there is more ivacaftor in Orkambi than in Kalydeco per dose. Perhaps like Jack Nicholson's character in *Five Easy Pieces*, who, when told he can't have a side order of toast, orders a chicken salad sandwich on toast and tells the waitress to "hold the chicken," patients with G551D should order lumacaftor-ivacaftor, but suggest "hold the lumacaftor" or just have the whole sandwich.

How did we get here? Prior to the discovery of the cellular defect and the CF gene and even since, our treatments have not been directed toward the basic defect but rather toward "downstream effects": tedious chest physical therapy to clear thick mucus from bronchi, antibiotics to treat bronchial infection caused by the infection-prone endobronchial milieu, pancreatic enzymes to replace those blocked by mucus-clogged pancreatic ducts. Things changed about 15 years ago, when the Cystic Fibrosis Foundation, a voluntary health organization founded in 1955 by parents frustrated by their children's horrendous quality and pitiably short length of life and continually supported over the ensuing 60 years by funds raised by CF families and

their friends, took an unprecedented and risky step: it invested some $75 million in Aurora Biosciences Corp, Cambridge, Massachusetts, a small biotech company, to encourage it to find a drug that would correct the basic cellular defect causing CF. Then, Vertex bought Aurora and continued the work, based on the science that had been developed by universities and Aurora and paid for by public funds (National Institutes of Health grants) and charitable donations. Finally, the work paid off—in scientific, clinical, and financial terms—with the licensing of Kalydeco. Vertex officials justify the sky-high price by pointing to the additional funds they supplied for research and development, the magnitude of the benefit to patients, and the small number of patients who qualify to use the drug (there are roughly 1200 patients in the United States with the G551D mutation and a smaller number who now qualify with mutations that cause related defects).

Some observers, ourselves included,[7] have attributed the price to the age-old price-setting standard in capitalism: "What the market will bear." So far in the United States, the market (private insurers and state health programs) has borne the price of Kalydeco with hardly a squeak.[8] Vertex executives have also pointed to their need to make the company profitable to satisfy their investors and have raised the specter of Vertex being bought out by a larger company less committed to developing new CF therapeutics. While not questioning their sincerity, some have been appalled by the windfall multimillion-dollar compensation packages the executive officers have managed for themselves,[9] raising eyebrows and ire over the huge prices for drugs that were developed through the work and sacrifice of patients and families, based substantially on science done with public funding and supported by the CF Foundation. The issue is complicated by the hundreds of millions of dollars coming back to the CFF in royalties from the sales of Kalydeco[10] and the $3.3 billion the foundation reaped from the sale of future royalties from this and other potential drugs.[11] The complication is the push-pull between the foundation's roles in advocating for patients (eg, need for affordable prices for CF drugs) and in securing funds for new research, better clinical care, and new drugs (need for more money from all sources, including royalties from drug sales). Opinions differ on how well the CFF has been and will be able to navigate these tricky shoals.

The problem of exceedingly high drug prices goes beyond CF. We have seen high prices for drugs targeting other conditions, including hepatitis C and various cancers. In 2014, all new FDA-approved cancer drugs were priced above $120 000 per year of use,[12] more than twice the average annual household gross income in the United States (which is about $52 000). (And, perhaps taking a page from Vertex and others, even manufacturers of inexpensive tried-and-true drugs are getting into the act: doxycycline, an antibiotic used for decades in CF, went from $20 a bottle in October 2013 to $1849 by April 2014.) Some doctors and hospitals have successfully pushed back. When Sanofi (Paris, France) introduced the colon cancer drug Zaltrap at about $11 000 a month, the staff at Memorial Sloan-Kettering Cancer Center in New York declined to stock the drug, pointing out that a drug already on their formulary was half the price and equally effective. Almost immediately, Sanofi cut the price of Zaltrap in half.[13] A recent commentary by more than 100 cancer specialists condemns the unconscionable prices for cancer drugs and the disconnect between drug costs and average patients' means and calls for a nationwide petition of protest.[12] These specialists hope to collect 1 million signatures, which will make their case heard and acted on. Perhaps they will succeed.

In CF, the situation is different. While there are millions of cancer patients, most of whom are old enough to vote, there are but 30 000 patients with CF in the country, and half are children. And unlike the situation with Sanofi's Zaltrap where there was competition, to date, there are no drugs competing with Vertex's Kalydeco and Orkambi. Although some companies are working on developing such drugs, for the time being, competitive pressures are absent. What about government intervention? Prices for drugs are dramatically more expensive in the United States than in any other developed country, largely because other countries have either a single (government) payer or regulations that cap prices. In the current political climate in the United States, this seems unlikely. The 2003 Medicare Prescription Drug, Improvement and Modernization Act, which established a prescription drug program for Medicare, expressly prohibited Medicare from negotiating drug prices with pharmaceutical companies, and attempts to rescind this legislation have been unsuccessful. The pharmaceutical industry pumps hundreds of millions of dollars each year into lobbying Congress and supporting congressional candidates.

To date, few if any patients in the United States have been unable to obtain their Kalydeco because either their insurance (private or state) covered it or Vertex's patient assistance program has helped with copays. It is too early to say if insurance companies and state programs will be as willing to cover the similarly high cost of Orkambi for some 10 times as many patients. If they do not, perhaps the uproar from patients and physicians will move regulators or Vertex to reconsider their pricing structure.

REFERENCES FOR THIS ARTICLE APPEAR ON PAGE 57.

To view or download the full-text article, visit: www.gahmj.com/doi/full/10.7453/gahmj.2015.123

REFERENCES FROM PAGE 9.

1. Dodge JA, Lewis PA, Stanton M, et al. Cystic fibrosis mortality and survival in the UK: 1947-2003. Eur Respir J. 2007;29:522-6.
2. Quinton PM, Bijman J. Higher bioelectric potentials due to decreased chloride absorption in the sweat glands of patients with cystic fibrosis. N Engl J Med 1983;308(20):1185-9.
3. Riordan JR, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science. 1989;245(4922):1066-73.
4. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR otentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med. 2011;365(18):1663-72.
5. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-Ivacaftor in patients with cystic fibrosis homozygous for phe508del CFTR. N Engl J Med. 2015;373(3):220-31.
6. Cholon DM, Quinney NL, Fulcher ML, et al. Potentiator ivacaftor abrogates pharmacological correction of DeltaF508 CFTR in cystic fibrosis. Sci Transl Med. 2014;6(246):246ra296.
7. O'Sullivan BP, Orenstein DM, Milla CE. Pricing for orphan drugs: will the market bear what society cannot? JAMA. 2013 Oct 2;310(13):1343-4.
8. Walker J. Arkansas reaches settlement in cystic fibrosis drug suit: state will revise eligibility criteria for renewing prescriptions for Vertex Pharmaceuticals' Kalydeco. Wall Street Journal. February 5, 2015. http://www.wsj.com/articles/arkansas-reaches-settlement-in-cystic-fibrosis-drug-suit-1423162197. Accessed September 23, 2015.
9. Weisman R. Cystic fibrosis drug could bring millions to executives: Critics decry plan to compensate Vertex executives if costly new drug is profitable. Boston Globe. May 1, 2015. https://www.bostonglobe.com/business/2015/04/30/bonuses-granted-senior-vertex-executives-are-increasingly-rare-compensation-specialists-say/QWQnwztbouoTYAER9ykhnJ/story.html. Accessed September 23, 2015.
10. Cohen D, Raftery J. Paying twice: questions over high cost of cystic fibrosis drug developed with charitable funding. BMJ. 2014;348:g1445.
11. Pollack A. Deal by Cystic Fibrosis Foundation raises cash and some concern. New York Times. November 19, 2014. http://www.nytimes.com/2014/11/19/business/for-cystic-fibrosis-foundation-venture-yields-windfall-in-hope-and-cash.html. Accessed September 23, 2015.
12. Tefferi A, Kantarjian H, Rajkumar SV, et al. In support of a patient-driven initiative and petition to lower the high price of cancer drugs. Mayo Clin Proc. Aug 2015;90(8):996-1000.
13. Pollack A. Sanofi halves price of cancer drug Zaltrap after Sloan-Kettering rejection. New York Times. November 8, 2012. http://www.nytimes.com/2012/11/09/business/sanofi-halves-price-of-drug-after-sloan-kettering-balks-at-paying-it.html?_r=0. Accessed September 23, 2015.