The Cystic Fibrosis 'explosion' - New medicines and unmet needs

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Summary

Cystic fibrosis (CF) is a multi-system illness caused by abnormalities in the CF transmembrane conductance regulator (CFTR) gene and protein. CFTR is an ion channel regulating transport of chloride, bicarbonate, and water, and influencing sodium resorption. Advances in CF care have led to dramatic increases in life expectancy and quality of life. We have entered an era of precision medicine, with therapy targeted to modify the CFTR protein, increasing production (premature termination codon read through), preventing degradation in the endoplasmic reticulum, improving folding, and chaperoning to the cell surface (correction), and increasing the open channel probability (potentiation). There are many new entrants into this therapeutic area, including combination therapy to enhance the recovery and effectiveness of ion transport through the most common CF gene defect – phe508del. Challenges for modulator therapies include targeting uncommon CFTR defects, assessing the long term effects of these therapies, and identifying clinical trial outcomes to evaluate the potential for very early therapy of infants with CF.

An additional need is effective immunomodulator therapy that can safely decrease the overwhelming neutrophil dominated inflammation that damages the CF airway. While glucocorticosteroids are effective in suppressing the eosinophil dominant inflammation characteristic of asthma, these appear to have little or no value in treating CF airway inflammation and their use comes at a significant cost in adverse events and current therapies for neutrophil dominant inflammation have limited effectiveness.

Introduction

Cystic fibrosis (CF) is a multi-system illness caused by abnormalities in the CF transmembrane conductance regulator (CFTR) gene and protein. CFTR is an ion channel regulating transport of chloride, bicarbonate, and water, and influencing sodium resorption. CF is inherited as an autosomal recessive disorder, and with about 70,000 CF patients worldwide, it is the most common life shortening disease among persons of European descent. Although there are more than 2,000 CFTR abnormalities reported - not all known to be disease causing - approximately 83% of patients with CF carry at least one phe508del allele. CFTR disease causing mutations are commonly classified into six classes depending on the mechanism of dysregulation (Table 1). These abnormalities can lead to complete failure to produce CFTR protein due to the presence of a premature termination codon, production of a misfolded and rapidly degraded CFTR (eg p.phe508del), and failure of the CFTR protein to effectively transport ions at the cell surface. In recent years, small molecule targeted therapy for specific classes of CFTR abnormalities have led to the development of CFTR potentiator medications that increase channel open probability enhancing chloride transport at the cell surface for Class III and Class IV defects, and CFTR correctors that decrease protein degradation for Class II defects like phe508del.

Therapy of cystic fibrosis

The major goal in treating CF is to clear the abnormal and excess secretions that lead to persistent airway infection and inflammation. For patients with advanced stages of disease, a lung transplant may be necessary. Treatment of gastrointestinal disease is also important. A diet rich in fat and protein, supplemented with digestive pancreatic enzymes for the 85% of patients who have pancreatic malabsorption, will lead to weight gain and better health outcomes. Because of fat malabsorption, the fat-soluble vitamins A, D, E, and K are supplemented using water soluble forms of these vitamins. Patients with significant hepatic dysfunction will benefit from therapy with medications such as ursodiol and those with CF related diabetes mellitus may require insulin supplementation to maintain health. Together, treatment of GI and pulmonary disease is the mainstay of the medical management of CF.

For pulmonary disease, therapy consists of early identification of chronic bacterial infection with attempts at eradication using both intravenous and inhaled antibiotics (1). There is an ongoing need to develop new antibiotics for the treatment of bacteria that eventually become resistant under pressure of chronic infection and intermittent antibiotic therapy. Chronic Pseudomonas aeruginosa infection is characteristic of CF, with over 90% of adult patients being chronically infected (not colonized) with this organism. However, data suggests that infection by multiply resistant Staphylococcus aureus may lead to a more rapid decline in lung function (2). Patients with CF are also prone to infection with resistant strains of Burkholderia cepacia, Stenotrophomonas maltophilia and Achromobacter xylosoxidans. By adulthood, many patients with CF are on chronic rotating cycles of inhaled antibiotics with intermittent therapy using high-dose oral or intravenous antibiotics to treat acute declines in pulmonary function and increase in cough and sputum reduction referred to as a pulmonary exacerbation.

Accompanying chronic infection is retention of infected sputum. The use of peptide mucolytic medications, such as Pulmozyme (dornase alfa) and expectorants (sometime referred to as hydrators) such as 7% inhaled hypertonic saline have become a mainstay of therapy. These therapies are usually administered in conjunction with airway clearance, maneuvers or devices that can include chest physical therapy, huff coughing, breathing maneuvers such as autogenic drainage, high frequency chest wall compression devices such as therapy Vests and airway positive expiratory pressure (PEP) or oscillating positive airway pressure (OPAP) devices (3). Hybrid devices that can produce a positive expiratory and allow inhalation of nebulized medications at the same time have more recently been introduced to the market.

Another important and unmet need is therapy to treat the chronic airway inflammation that accompanies this infection. There is evidence that inflammatory response in the CF airway is dysregulated with failure to resolve a predominantly neutrophilic inflammation leading to an extensive neutrophil necrosis and NETosis. Although medications such as corticosteroids are often used, these are ineffective in treating neutrophil dominated inflammation. Ibuprofen therapy for neutrophilic inflammation was introduced some two decades ago but is used in few centers because of the need for careful monitoring of serum levels. Chronic low dose 14- and 15-member macrolide antibiotics are immunomodulatory medications primarily acting through the extracellular signaling regulated kinase to decrease neutrophil dominated inflammation (4). Most commonly used in CF is azithromycin, given three times a week as a chronic therapy. This inevitably leads to macrolide resistant organisms including atypical Mycobacteria. Thus, there is an unmet need for effective anti-inflammatory medications that can be given chronically, safely, and will not stimulate antimicrobial resistance.

CFTR modulator therapy

CFTR modulator medications include potentiators, such as ivacaftor that increase channel opening probability when even a defective CFTR is chaperoned to the airway surface (5), premature termination codon, read through medications, and corrector medications such as lumacaftor that will prevent endoplasmic reticulum degradation of abnormally folded CFTR protein permitting more of this protein to come to the airway surface where a concomitantly administered potentiator can increase the channel open probability (6).

The first of these medications was ivacaftor, sold as Kalydeco (Vertex Pharmaceuticals). It is a small molecule orally administered potentiator of CFTR channel function active against Class III and Class IV CFTR mutations. In patients with these mutations, ivacaftor is as close as we have seen to a cure for C, producing significant improvement in pulmonary function, normalization of sweat chloride, improved weight gain, decreased airway inflammation, and decreased airway infection. However, low grade infection with bacteria such as Pseudomonas persists meaning that the need for antimicrobial therapy is not obviated even in patients who have a dramatic clinical response to ivacaftor. The combination of ivacaftor and lumacaftor (Orkambi – Vertex Pharmaceuticals) in patients who are homozygous for the phe508del CFTR mutation, has been shown to improve nutritional status, decrease the rate of pulmonary exacerbation, and decrease the rate of lung function decline by over 40% over a period of 2 years of therapy (7).

The second combination CFTR modulator of Tezacaftor (corrector) and /ivacaftor was approved in the United States in February 2018 and is marketed as Symdeko. Unlike Orkambi, Symdeko is approved for both patients over the age of 12 years who are homozygous and heterozygous for phe508del. Symdeko is reported to improve pulmonary function as least as well as Orkambi and appears to have fewer side effects – in particular the flu-like illness with chest tightness that has been reported in up to 20% of patients when starting Orkambi. This chest discomfort and dyspnoea is more common in patients with more severe lung disease.

Triple therapy is also in late stage clinical trials combining and early corrector (designated C1) and a late or C2 corrector with a potentiator. These include VX-445 + tezacaftor + ivacaftor, VX-659 + tezacaftor + ivacaftor, as well as early phase clinical trials by Vertex, Galapagos/AbbiVie. Recently guidelines for the use of CFTR modular therapy have been published (8) however this is so rapidly changing that updates may be needed as often as annually. There are also trials of inhibitors of the epithelial sodium channel (ENaC) that is overactive when CFTR is dysfunctional, CFTR mRNA delivery, and oligonucleotide therapy to repair CFTR mRNA. Most of these are orally administered therapies. Beyond these innovations are trials of new inhaled antibiotics, bacterial biofilm disrupters, and anti-inflammatory medications.

Fifteen years ago, an editorial was published in the journal CHEST entitled "So many drugs, so little time. The future challenge of cystic fibrosis care" (9). Fifteen years on this is truer than ever (Figure 1). Unfortunately, the therapeutic burden for patients with CF is already quite complex, taking up a great deal of time. It has been shown that adherence to prescribe therapy is inversely correlated with therapeutic burden. Thus, studies are urgently needed to see if patients can safely discontinue some of their existing therapies as these new medications are added. The ultimate goal is to find a cure for CF, perhaps by adopting gene editing techniques to correct this autosomal recessive, monogenetic defect.

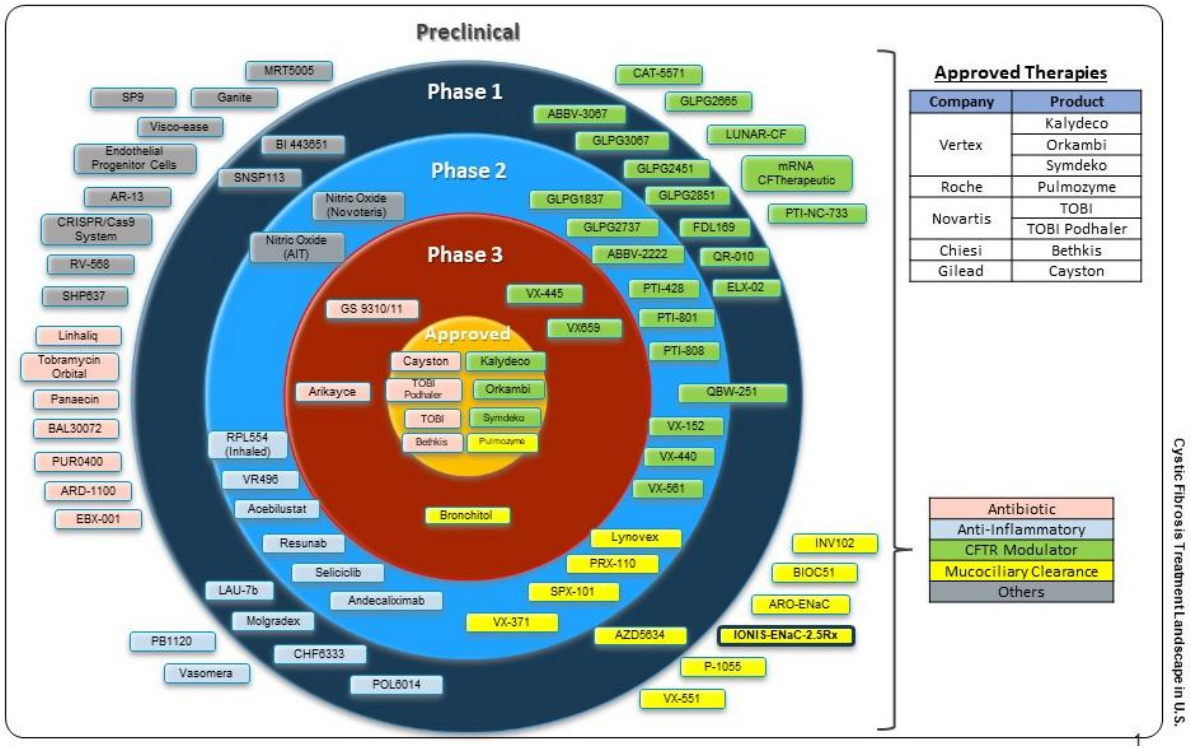

Figure 1: CF Treatment Landscape U.S.

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