



Case Report

Treating Non-cystic Fibrosis Bronchiectasis with CFTR modulators: Early Case Reports

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Abstract

Non-cystic fibrosis bronchiectasis (NCFB) afflicts millions of patients worldwide, with few drug therapies that address underlying pathogenic mechanism. Despite the time-honoured view that NCFB is unrelated to cystic fibrosis (CF), growing evidence indicates many patients with NCFB exhibit functional deficiency of the cystic fibrosis transmembrane conductance regulator (CFTR). We investigated whether modulator compounds that activate both wild-type and mutant CFTR could improve clinical status in certain patients with NCFB, and explored the relationship(s) between CFTR and NCFB. High cost of CFTR modulators such as elexacaftor/tezacaftor/ivacaftor (ETI; ~\$300,000/year) largely precludes "off label" prescribing, making a test of CFTR activation in patients with NCFB problematic. Special efforts were therefore made to administer ETI in three patients with severe NCFB. Marked improvements in clinical status (pulmonary function, symptom scores, chest imaging) were observed. These patients were representative of individuals with NCFB followed in general practice and/or pulmonary clinics and are among the first reported with NCFB to be treated successfully with CFTR modulators. ETI would not have been considered part of standard care, even in the setting of severe clinical disease. CF genotype, in vivo CFTR activity (sweat chloride analysis), and in vitro (cell-based) CFTR functional reserve were also assessed in the context of non-CF and CF-related bronchiectasis. Available literature and present findings support a need for future studies to examine and validate clinically meaningful association(s) between NCFB and CFTR. Investigations of this sort are expected to have important mechanistic, diagnostic, and therapeutic implications for many patients with non-CF bronchiectasis.

Keywords: CFTR deficiency; CFTR modulator treatment; Cystic fibrosis; Diagnostic procedures for NCFB; Non-cystic fibrosis bronchiectasis

Introduction

NCFB and relationship to cystic fibrosis

Non-cystic fibrosis bronchiectasis (NCFB) is characterized by abnormal dilation of the airways, impaired mucociliary clearance (MCC), and recurrent polymicrobial lung infection. Resultant inflammation and endobronchial damage culminate in further loss of pulmonary reserve. The etiology of NCFB is poorly understood, but believed to be heterogeneous, reflecting a number of distinct respiratory insults, as well as other consequential influences [1-3].

Like NCFB, cystic fibrosis (CF) bronchiectasis is associated with structural dilatation of the airways, mucus stasis, chronic bacterial infection, persistent inflammation, lung tissue remodelling, and diminished respiratory function [1-6]. CF is an autosomal recessive illness attributable to absence or dysregulation of the cystic fibrosis transmembrane conductance regulator (CFTR), an epithelial ion channel situated within apical membranes of secretory epithelium and essential for mucociliary clearance by the lung.

CF is usually identified by findings such as elevated sweat chloride (≥ 60 mEq/L in most diagnosed cases), two disease-causing CFTR mutations, exocrine disorders in one or more organs, or a combination of the above. Patients with NCFB (by definition) do not have clinical criteria sufficient for a diagnosis of CF, and NCFB historically has been viewed as independent of CFTR. That being said, heterozygous (silent) carriers of CFTR mutations (i.e., individuals with one CFTR variant and one wild-type allele) are at increased risk for developing NCFB [7-10]. Moreover, chronic inflammation, hypoxia, exposure to cigarette smoke, and other environmental factors contribute to acquired CFTR deficiency in lung illnesses such as NCFB [11,12], and one study indicates upwards of 20% of the non-cystic fibrosis bronchiectasis population exhibit partial loss of airway CFTR activity[11].

Highly effective CFTR modulator treatments (HEMTs) such as elexacaftor/tezacaftor/ivacaftor (ETI) have been shown to provide dramatic benefit among patients with CF [13-17]. Modulators work by augmenting biogenesis, maturation, and/or gating of the CFTR ion channel. Based on an increasing body of evidence, we pursued the hypothesis that certain patients with otherwise poorly treatable NCFB might demonstrate clinical improvement from compounds that activate CFTR. That notion has not been adequately proposed or tested, although scientific and mechanistic rationale are strong.

As a first step, we investigated whether modulators that activate both wild-type and mutant CFTR would improve NCFB clinical status. Below, we describe some of the first NCFB patients (selected based on presence of a single F508del CFTR mutation)

treated chronically with ETI. These individuals are representative (in a “real world” sense) of NCFB patients followed by general practice and/or subspecialty/referral clinics (and for whom CFTR mutations have been reported to occur in 30-40% [11,18]). Importantly, ETI would not otherwise have been considered as part of standard care for such individuals, even in the setting of severe clinical disease. Because high cost restricts “off-label” (including non-CF) prescribing of modulators, efforts were made to obtain and evaluate ETI in case studies of three patients with chronic and progressive NCFB.

Case 1

A 62-year-old female with a diagnosis of NCFB and refractory nontuberculous mycobacterial lung disease (NTM-LD) was referred for evaluation. Twelve years earlier, the patient completed 18 months of daily ethambutol, rifampin and azithromycin for treatment of *M. avium* complex (MAC). Approximately eight years prior to referral, sputum grew *M. abscessus* complex, and clofazimine, amikacin, tigecycline, and imipenem-cilastatin were administered for six months, followed by clofazimine, azithromycin, bedaquiline, and nebulized amikacin for an additional twelve months. The patient subsequently experienced 20-pound weight loss, daily low-grade fevers, and intermittent hemoptysis. CT imaging demonstrated NCFB (Figure 1A). During follow-up, further weight loss and productive cough were noted. In addition to positive mycobacterial cultures, sputum grew *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa*. At presentation to our clinic, and in an attempt to eradicate *P. aeruginosa*, 14 days of levofloxacin and 60 days of nebulized tobramycin were initiated. While sputum production and hemoptysis improved, weight loss, fatigue, and low-grade fever persisted. COPD Assessment Test (CAT) [19] score was 27, indicating a considerable symptom burden. Forced expiratory volume in 1 second (FEV1) and body mass index (BMI) were significantly decreased (Table 1). Immunoglobulins, alpha 1 antitrypsin level, and autoimmune testing were unrevealing, whereas CFTR genotype demonstrated a single copy of F508del following complete CFTR DNA sequencing.

In the setting of declining clinical status, refractory NTM, and ongoing infections with gram-negative pathogens, and based on F508del carrier status, ETI was initiated. At follow-up three months later, the patient reported near total resolution of prior respiratory and constitutional symptoms. She retained mild intermittent cough without significant sputum production. There was no further hemoptysis, fever, or weight loss, and BMI increased. CAT score was 10, reflecting a substantial quality-of-life response. CT imaging revealed less mucus impaction, diminished tree-in-bud nodularity, and decreased air trapping (Figure 1B). The pronounced symptomatic and clinical benefit observed at month three of treatment have persisted to one-year while continuing

ETI, with considerable improvement of FEV1.

Case 2

A 63-year-old female with a 15-year history of NCFB and sputum positivity for MAC and *Pseudomonas aeruginosa* had been treated for 18 months with clarithromycin, ethambutol, and moxifloxacin. Sputum became negative for MAC, but continued to grow *P. aeruginosa*, as well as *Aspergillus fumigatus*, *Scedosporium apiospermum*, and methicillin sensitive *Staphylococcus aureus* (MSSA). Oral antibiotics (e.g., fluoroquinolones) were administered intermittently for eight years, together with two courses of itraconazole. Upon transfer to our clinic six years ago, the patient reported daily cough productive of green sputum and hemoptysis. She also complained of fatigue, dyspnea on exertion, and recurrent low-grade fever. CAT score was 25, reflecting high disease burden. Laboratory evaluation revealed a single copy of F508del CFTR (from a screen for 165 CFTR variants), and respiratory culture yielded two isolates of mucoid *P. aeruginosa* (fluoroquinolone resistant). The patient was prescribed cycled nebulized tobramycin, but CAT scores remained elevated, with sputum that continued to grow *P. aeruginosa*, MSSA, and *Aspergillus* species. MAC was consistently isolated from surveillance respiratory cultures, with worsening of clinical symptoms and diagnostic radiographic findings (Figure 1C). Treatment was initiated with a combination of daily azithromycin, ethambutol and clofazimine due to rifamycin intolerance. Fever resolved and cough improved, but fatigue, weight loss, and intermittent hemoptysis persisted.

Based on severe pulmonary insufficiency and debilitating infection despite aggressive antimicrobial therapy, the patient was prescribed ETI. At follow-up visit two months later, all symptoms had markedly improved, with CAT score falling to 9. Spirometry and BMI increased (Table 1), and radiographic improvement was noted (Figure 1D). These favourable findings have been maintained at 12-months on ETI.

Case 3

A 57-year-old man presented with an eight-year history of NCFB and exhibited sputum cultures positive for methicillin-

resistant *staphylococcus aureus* (MRSA) and *Mycobacterium abscessus massiliense*. CT scan demonstrated moderate cylindrical bronchiectasis and tree-in-bud infiltrates affecting both upper lobes, right middle lobe and superior segments of the right and left lower lobes. Spirometry demonstrated an FEV1 of 2.92 L (89% of predicted). Complete CFTR DNA sequencing revealed a single copy of F508del. Sweat chloride levels were 25-28 mEq/L, and fecal elastase was within normal limits. The patient was started on airway clearance therapy with a flutter valve and hypertonic saline, but experienced worsening of cough, and sputum cultures remained positive for MRSA. Treatment with doxycycline conferred minimal benefit. Repeat chest CT demonstrated NCFB progression with new areas of nodularity and airway impaction in the left upper and right middle lobes. Sputum grew *Mycobacterium abscessus* complex and FEV1 continued to decrease. Anti-mycobacterial treatment led to improvements in cough, fatigue, and dyspnea, with sputum negative for acid-fast bacilli (AFB). The patient remained on antimicrobials for 12 additional months, at which point cultures were found to contain *Pseudomonas aeruginosa*, *Pseudomonas putida*, *Stenotrophomonas* and *Aspergillus*, together with reappearance of *Mycobacterium abscessus* complex. This coincided with increased cough and sputum production.

A trial of ETI was undertaken when spirometry (FEV1 2.36 L; 76% predicted), BMI, and clinical trajectory were deteriorating (Table 1). One week after starting CFTR modulator therapy, the patient reported improved breathing, diminished cough, and “thick yellow” sputum had become “thin and clear.” Fatigue diminished and exertional capacity increased. Spirometry and BMI improved (Table 1). Moderate indirect hyperbilirubinemia (a recognized side effect of ETI) was observed, with normal LDH, haptoglobin and transaminases. HEMT dose was adjusted with stabilization of bilirubin levels and the patient continued on ETI. Bronchiectasis Severity Index (BSI) scores improved from 8 to 3 following initiation of modulator therapy. Subsequent sputum cultures over the next 16 months (while on ETI) have remained negative for MRSA, mycobacterium, and *Pseudomonas*, with respiratory symptoms continuing to benefit and FEV1 remaining stable.

Case	Sex	FEV1 Pre-ETI	FEV1 Post-ETI	BMI Pre-ETI	BMI Post-ETI
1	F	1.64 (66%)	1.86 (76%)	17.8	21.3
2	F	0.65 (29%)	0.82(35%)	18.8	19.9
3	M	2.36 (76%)	2.45 (81%)	24.6	25.1

Table 1: FEV1 (in L(%predicted)) and BMI (kg/m²) before and after ETI treatment.

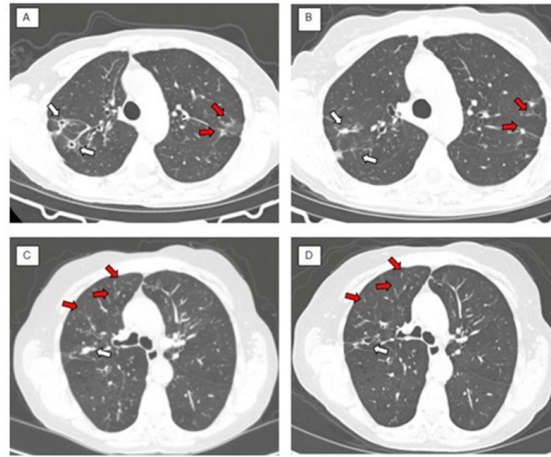


Figure 1: CT chest images for cases 1 (A & B) and 2 (C & D). (A) CT scan pre-ETI demonstrates cavitory lesions in right upper lobe (white arrows) and inflammatory changes in left upper lobe (red arrows). (B) CT chest image post-ETI showing closure of cavitory lesions (white arrows) and cicatricial healing in left upper lobe (red arrows). (C) Axial CT image before ETI. Note mucus impaction (white arrow) and tree-in-bud nodularity in the right upper lobe (red arrows). (D) After ETI, improvement in mucus impaction was observed (white arrow) together with resolution of tree-in-bud nodularity (red arrows).

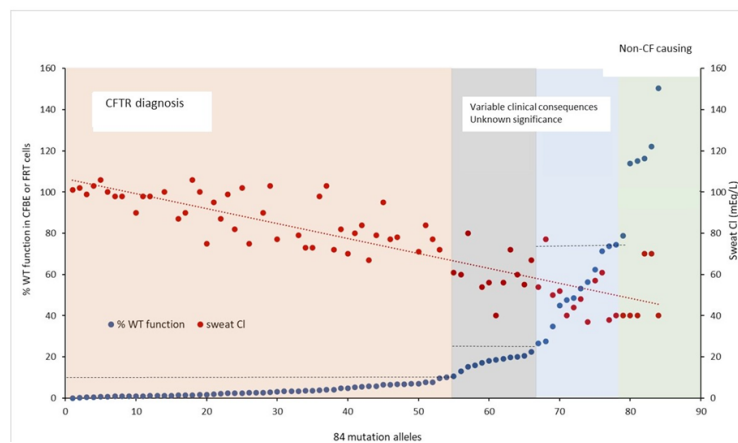


Figure 2: CFTR-related lung disease in relation to functional CFTR reserve. Clinical data shown is from the CFTR2 database (<https://cftr2.org/>) or cell models reported by Han et al. [20]. Findings describe 84 CFTR mutations ranked according to in vitro activity. Sweat chloride values are based on patients in which the second CFTR variant encodes a mutation with minimal function. In that scenario, sweat chloride of 30-59 mEq/L is often associated with bronchiectasis and can be viewed as a risk factor for CFTR-deficient lung disease. “Variable clinical consequences/Unknown significance” includes patients with bronchiectasis but clinical findings inadequate to establish a complete CF phenotype. FRT: Fischer rat thyroid cells. CFBE: cystic fibrosis bronchial epithelium. Horizontal dashed lines represent upper threshold of CFTR activity in relation to wild-type CFTR in cell lines for each diagnostic group.

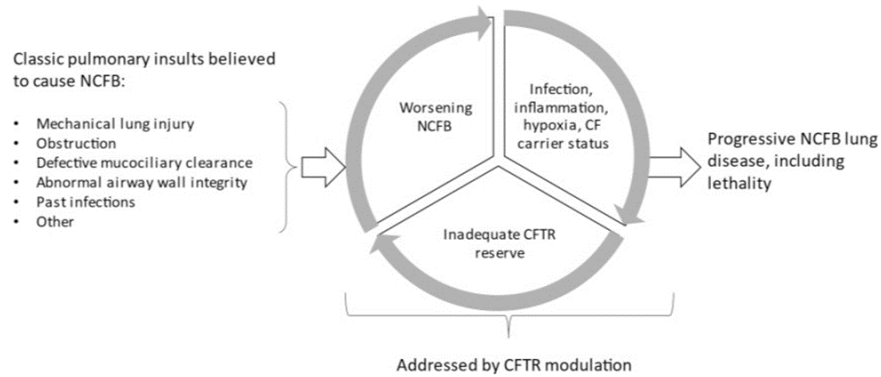


Figure 3: Mechanism of NCFB pathogenesis.

Results and Discussion

CFTR deficiency exists along a continuum in patients with bronchiectasis

One can argue that discriminating between clinically important subtypes of bronchiectasis might be improved by considering the extent to which CFTR is functionally available. For many patients with a diagnosis of bronchiectasis, both sweat chloride and CFTR ion channel activity (using cell systems relevant to FDA modulator approval) are known to distribute across a spectrum (Figure 2) [20]. Such findings are in agreement with earlier reports [7-11,18], and support the notion that patients with NCFB are often deficient for CFTR and could benefit from ETI (which robustly activates both the mutant and wild-type CF gene product).

Diagnostic considerations

Testing for CFTR reserve is not typically performed as part of standard management for patients with NCFB. If a person with bronchiectasis is older and lacks extra pulmonary manifestations of cystic fibrosis, the diagnosis of NCFB is commonly applied. We suggest that diagnostic criteria for NCFB would be enhanced by expanded monitoring for CFTR deficiency (e.g., as judged by mutation analysis, elevated sweat chloride, or in vivo bioelectric measurements). The latter interpretation has already been acknowledged for individuals who exhibit an incomplete CF phenotype (i.e., CFTR-related disorder [21]), where CF-like disease is often observed in only one organ, such as lung or pancreas. Importantly, among patients with CFTR-related disorder, a single F508del mutation does not allow access to CFTR modulators. The drug is costly—and “off label” use (for patients without a formal diagnosis of cystic fibrosis)—is not typically reimbursable by insurers. That said, individuals with CFTR-related disorder commonly exhibit evidence of both CFTR deficiency and bronchiectasis, and there is every reason to believe that respiratory

improvement would result in many such patients using ETI. From the standpoint of a much larger patient population, the label of “non-CF bronchiectasis” is often assigned (in general medical and pulmonary clinics worldwide) without evaluating either CFTR genotype or sweat chloride, and a diagnosis of NCFB largely precludes treatments such as ETI. This is despite the fact that a genotype encoding a single CFTR mutation such as F508del is more common in patients with NCFB and is clearly associated with pathogenesis [7-9,11,18]. Although mechanistic overlap surely exists between many cases of CFTR-related disorder and NCFB, ETI has never been evaluated in controlled studies for either condition. We believe rigorous trials to investigate CFTR modulators in these settings are indicated.

Caveats regarding ETI as a potential intervention for NCFB

Case study data as presented in the current report should be viewed with circumspection. The patients described here were all characterized by a correct diagnosis of NCFB according to established guidelines and exhibited non-CF genotype, age >55, absence of extra pulmonary manifestations of CF, progressively worsening lung disease, unambiguous symptomatic benefit following modulator treatment, and FEV1 improvement from ETI comparable to (or above) what has been achieved previously using early generation (FDA approved) CFTR modulators for cystic fibrosis [22-24]. Medical clinics internationally follow large numbers of individuals with NCFB diagnosed and managed in the same manner as those reported here—but without consideration of CFTR genotype testing or treatment with ETI. This traditional approach to NCFB diagnosis and management has been acceptable in part because interventions for addressing CFTR deficiency were not available, and determination of adequate CFTR function therefore was not pursued. With the advent of highly effective modulator treatments (and if future studies confirm results

presented above), we suggest a standard NCFB diagnosis would be aided by including an assessment of CFTR reserve.

Relevance of drug cost

The high price of CFTR modulators prevents ETI access globally among patients with NCFB, CFTR-related disorder, and many patients with CF. While modulator treatment is well tolerated in most individuals with cystic fibrosis (as well as the NCFB patients described in this report), future clinical trials [25,26] in much larger numbers of subjects will be needed to evaluate safety and efficacy among those with NCFB, and to determine the extent to which this patient population might benefit. At least in principle, successful studies of this type could also impact the high cost of ETI therapy by significantly expanding market size.

Conclusions

Hundreds of thousands of individuals with NCFB worldwide who receive standard medical care have not been evaluated for partial CFTR deficiency. Compelling evidence suggests that a subset of such individuals might benefit from CFTR activation and the associated increase in MCC. Modulator responsiveness for NCFB has not been adequately considered, in part because the two diseases (NCFB and CF) have been viewed as mechanistically distinct and mutually exclusive. Many tertiary care referral programs such as ours have begun testing whether patients with NCFB and one F508del CFTR mutation can experience lung function improvement using ETI, and a refined mechanistic understanding of the disease is likely to result (Figure 3). The same interpretation is already acknowledged for management of individuals with bronchiectasis who meet criteria for an incomplete CF phenotype. If the current hypothesis and findings are validated among larger numbers of individuals with NCFB, the data will offer new therapeutic considerations for patients with an otherwise poorly treatable and progressive lung disease.

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Conflict of Interest: The authors declare no financial conflict of interest.

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