Preface

Cystic Fibrosis in the Era of Highly Effective CFTR Modulators

Clemente J. Britto, MD, ATSF Jennifer L. Taylor-Cousar, MD, MSCS, ATSF

Editors

Cystic fibrosis (CF) was described as a clinical entity more than eighty years ago.[1–3] With the development of comprehensive care centers and therapies directed at the signs and symptoms of the disease, survival improved.[4] What once was a disease only of children has become a chronic disease of adults for whom the median predicted survival is fifty years of age.[5,6] As the natural history of CF has evolved, so has the recognition of previously underdiagnosed populations of people with CF, contributing to its rising prevalence around the world.[7–10]

We are in the midst of a new era in CF care ushered in by the advent of cystic fibrosis transmembrane conductance regulator (CFTR) modulators, small molecules that significantly restore CFTR protein function. People with CF are experiencing marked rapid and sustained improvements in lung function, nutritional state, and quality of life.[11–13] With the approval of the first triple-modulator combination, elexacaftor/tezacaftor/ivacaftor, for people with CF with at least one copy of the most common CF mutations in those of European ancestry, *Phe508del* (*F508del*), approximately 90% of the CF population is now eligible for highly effective modulator therapy (HEMT) and its associated transformational health benefits.[13]

Since the previous CF-focused issue of *Clinics in Chest Medicine*,[14] there have been broad advances in our understanding of the immunopathogenesis of CF and the remarkable impact of modulators on immune cell function, inflammation, and repair mechanisms.[15–17] Indeed, the CFTR correction afforded by HEMT is increasingly recognized as a modifying factor in the microbiome and airway inflammatory response of people with CF.[18–22]

Advances have also emerged in animal models, cell-based assays, and approaches to measure and titrate functional responses to modulators in human tissues and cells.[23–26] Emerging tools, such as novel pulmonary function measures, pulmonary imaging, patient-reported outcomes, and new molecular biomarkers, will become increasingly important in understanding CF pathogenesis and treatment response.[27–34]

Apart from the well-documented impact of HEMT on lung function and nutritional outcomes, HEMT promises to have extensive effects in multiple areas of clinical care. Emerging reports of effects range from changes in airway microbial

Clin Chest Med 43 (2022) xiii–xvi
https://doi.org/10.1016/j.ccm.2022.07.003
0272-5231/22/

communities with associated opportunities for developing novel antimicrobial therapies, evolving knowledge regarding the surveillance and management of long-term endocrine and gastrointestinal complications, and new opportunities in family planning and reproductive health.[35–41]

HEMT has had a transformative effect on the lives of many people with CF. However, some questions remain to be answered. For example, there are ongoing efforts to develop safe and effective readthrough agents and the next generation of modulators and immunomodulatory drugs for those ineligible for or intolerant of currently approved HEMT. Ultimately, gene replacement or editing will be necessary to cure CF.[42–47] We speculate that one day we will be able to turn back the clock on the development of clinical disease through very early intervention; such intervention is currently being investigated in animal models of CF and in trials of HEMT administration in infants and toddlers.[48,49] Finally, although we anticipate that recent advances will result in a smaller proportion of people with CF requiring lung transplantation or end-of-life care,[50] the CF community remains committed to optimizing care for each individual with CF.

In this issue of *Clinics in Chest Medicine*, we take stock of the gains enabled by the development of HEMT and consider the remaining challenges to assessing and improving the quantity and quality of life for all people with CF. As the clinical course and management of CF evolve in this new therapeutic era, we look forward to a promising and bright future in which CF-related morbidity is rare, health is maintained, and CF finally becomes a curable disease.

Clemente J. Britto, MD, ATSF
Department of Internal Medicine
Division of Pulmonary, Critical Care
and Sleep Medicine
Yale University School of Medicine
300 Cedar Street, TAC-S419
New Haven, CT 06520, USA

Jennifer L. Taylor-Cousar, MD, MSCS, ATSF
Departments of Medicine and Pediatrics
Divisions of Pulmonary Sciences and
Critical Care Medicine and Pediatric Pulmonology
University of Colorado
Anschutz Medical Campus
1400 Jackson Street, J318
Denver, CO 80206, USA

E-mail addresses:
clemente.britto@yale.edu (C.J. Britto)
taylorcousarj@njhealth.org (J.L. Taylor-Cousar)

REFERENCES

1. 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.
2. Davis PB. Cystic fibrosis since 1938. Am J Respir Crit Care Med 2006;173(5):475–82.
3. Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study. Am J Dis Child 1938;56(2):344–99.
4. Patient Registry. Cystic Fibrosis Foundation. Available at: https://www.cff.org/medical-professionals/patient-registry. Accessed March 29, 2022.
5. McKone EF, Ariti C, Jackson A, et al. Survival estimates in European cystic fibrosis patients and the impact of socioeconomic factors: a retrospective registry cohort study. Eur Respir J 2021;58(3). https://doi.org/10.1183/13993003.02288-2020.
6. Stephenson AL, Sykes J, Stanojevic S, et al. Survival Comparison of Patients With Cystic Fibrosis in Canada and the United States: A Population-Based Cohort Study. Ann Intern Med 2017;166(8): 537–46.
7. Hamosh A, FitzSimmons SC, Macek M Jr, et al. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. J Pediatr 1998; 132(2):255–9.
8. Powers CA, Potter EM, Wessel HU, et al. Cystic fibrosis in Asian Indians. Arch Pediatr Adolesc Med 1996;150(5):554–5.
9. Yamashiro Y, Shimizu T, Oguchi S, et al. The estimated incidence of cystic fibrosis in Japan. J Pediatr Gastroenterol Nutr 1997;24(5):544–7.
10. Stafler P, Mei-Zahav M, Wilschanski M, et al. The impact of a national population carrier screening program on cystic fibrosis birth rate and age at diagnosis: Implications for newborn screening. J Cyst Fibros 2016;15(4):460–6.
11. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011;365(18): 1663–72.
12. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. N Engl J Med 2017; 377(21):2013–23.
13. 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):1809–19.
14. Koff J. Cystic Fibrosis, an Issue of Clinics in chest medicine. Elsevier Health Sciences; 2016.
15. Gillan JL, Davidson DJ, Gray RD. Targeting cystic fibrosis inflammation in the age of CFTR modulators: focus on macrophages. Eur Respir J 2021;57(6). https://doi.org/10.1183/13993003.03502-2020.

16. Hisert KB, Birkland TP, Schoenfelt KQ, et al. Ivacaftor decreases monocyte sensitivity to interferon-γ in people with cystic fibrosis. ERJ Open Res 2020;6(2). https://doi.org/10.1183/23120541.00318-2019.
17. Jarosz-Griffiths HH, Scambler T, Wong CH, et al. Different CFTR modulator combinations downregulate inflammation differently in cystic fibrosis. Elife 2020;9. https://doi.org/10.7554/eLife.54556.
18. Harris JK, Wagner BD, Zemanick ET, et al. Changes in Airway Microbiome and Inflammation with Ivacaftor Treatment in Patients with Cystic Fibrosis and the G551D Mutation. Ann Am Thorac Soc 2020;17(2):212–20.
19. Grasemann H, Gonska T, Avolio J, et al. Effect of ivacaftor therapy on exhaled nitric oxide in patients with cystic fibrosis. J Cyst Fibros 2015;14(6):727–32.
20. Green M, Lindgren N, Henderson A, et al. Ivacaftor partially corrects airway inflammation in a humanized G551D rat. Am J Physiol Lung Cell Mol Physiol 2021;320(6):L1093–100.
21. Barnaby R, Koeppen K, Nymon A, et al. Lumacaftor (VX-809) restores the ability of CF macrophages to phagocytose and kill Pseudomonas aeruginosa. Am J Physiol Lung Cell Mol Physiol 2018;314(3):L432–8.
22. Ruffin M, Roussel L, Maillé É, et al. Vx-809/Vx-770 treatment reduces inflammatory response to Pseudomonas aeruginosa in primary differentiated cystic fibrosis bronchial epithelial cells. Am J Physiol Lung Cell Mol Physiol 2018;314(4):L635–41.
23. Clancy JP, Cotton CU, Donaldson SH, et al. CFTR modulator theratyping: Current status, gaps and future directions. J Cyst Fibros 2019;18(1):22–34.
24. Pedemonte N, Zegarra-Moran O, Galietta LJV. High-throughput screening of libraries of compounds to identify CFTR modulators. Methods Mol Biol 2011;741:13–21.
25. Sui J, Cotard S, Andersen J, et al. Optimization of a Yellow fluorescent protein-based iodide influx high-throughput screening assay for cystic fibrosis transmembrane conductance regulator (CFTR) modulators. Assay Drug Dev Technol 2010;8(6):656–68.
26. Liang F, Shang H, Jordan NJ, et al. High-Throughput Screening for Readthrough Modulators of CFTR PTC Mutations. SLAS Technol 2017;22(3):315–24.
27. Horsley AR, Belcher J, Bayfield K, et al. Longitudinal assessment of lung clearance index to monitor disease progression in children and adults with cystic fibrosis. Thorax 2021. https://doi.org/10.1136/thoraxjnl-2021-216928.
28. Smith L, Aldag I, Hughes P, et al. Longitudinal monitoring of disease progression in children with mild CF using hyperpolarised gas MRI and LCI. Eur Respir J 2016;48(suppl 60). https://doi.org/10.1183/13993003.congress-2016.OA284.
29. Szczesniak R, Turkovic L, Andrinopoulou ER, et al. Chest imaging in cystic fibrosis studies: What counts, and can be counted? J Cyst Fibros 2017;16(2):175–85.
30. Dournes G, Walkup LL, Benlala I, et al. The Clinical Use of Lung MRI in Cystic Fibrosis: What, Now, How? Chest 2021;159(6):2205–17.
31. Beswick DM, Humphries SM, Balkissoon CD, et al. Impact of CFTR Therapy on Chronic Rhinosinusitis and Health Status: Deep Learning CT Analysis and Patient Reported Outcomes. Ann Am Thorac Soc 2021. https://doi.org/10.1513/AnnalsATS.202101-057OC.
32. Sathe M, Moshiree B, Vu PT, et al. Utilization of electronic patient-reported outcome measures in cystic fibrosis research: Application to the GALAXY study. J Cyst Fibros 2021;20(4):605–11.
33. Ishak A, Stick SM, Turkovic L, et al. BAL Inflammatory Markers Can Predict Pulmonary Exacerbations in Children With Cystic Fibrosis. Chest 2020;158(6):2314–22.
34. Khanal S, Webster M, Niu N, et al. SPLUNC1: a novel marker of cystic fibrosis exacerbations. Eur Respir J 2021. https://doi.org/10.1183/13993003.00507-2020.
35. Payne JE, Dubois AV, Ingram RJ, et al. Activity of innate antimicrobial peptides and ivacaftor against clinical cystic fibrosis respiratory pathogens. Int J Antimicrob Agents 2017;50(3):427–35.
36. Volkova N, Moy K, Evans J, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries. J Cyst Fibros 2020;19(1):68–79.
37. Shteinberg M, Taylor-Cousar JL, Durieu I, et al. Fertility and Pregnancy in Cystic Fibrosis. Chest 2021. https://doi.org/10.1016/j.chest.2021.07.024.
38. Freeman AJ, Sathe M, Aliaj E, et al. Designing the GALAXY study: Partnering with the cystic fibrosis community to optimize assessment of gastrointestinal symptoms. J Cyst Fibros 2021;20(4):598–604.
39. Smith S, Rowbotham NJ, Regan KH. Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis. Cochrane Database Syst Rev 2018;3(3):CD001021.
40. Abdalla MY, Switzer BL, Goss CH, et al. Gallium Compounds Exhibit Potential as New Therapeutic Agents against Mycobacterium abscessus. Antimicrob Agents Chemother 2015;59(8):4826–34.
41. Chan BK, Stanley G, Modak M, et al. Bacteriophage therapy for infections in CF. Pediatr Pulmonol 2021;56(Suppl 1):S4–9.
42. Christopher Boyd A, Guo S, Huang L, et al. New approaches to genetic therapies for cystic fibrosis. J Cyst Fibros 2020;19:S54–9.
43. Pranke I, Golec A, Hinzpeter A, et al. Emerging Therapeutic Approaches for Cystic Fibrosis. From Gene Editing to Personalized Medicine. Front Pharmacol 2019;10:121.

44. Lueck JD, Yoon JS, Perales-Puchalt A, et al. Engineered transfer RNAs for suppression of premature termination codons. Nat Commun 2019; 10(1):822.
45. Crane AM, Kramer P, Bui JH, et al. Targeted correction and restored function of the CFTR gene in cystic fibrosis induced pluripotent stem cells. Stem Cell Rep 2015;4(4):569–77.
46. Xia E, Zhang Y, Cao H, et al. TALEN-Mediated Gene Targeting for Cystic Fibrosis-Gene Therapy. Genes 2019;10(1). https://doi.org/10.3390/genes10010039.
47. King NE, Suzuki S, Barillà C, et al. Correction of Airway Stem Cells: Genome Editing Approaches for the Treatment of Cystic Fibrosis. Hum Gene Ther 2020;31(17–18):956–72.
48. Egan ME. Cystic fibrosis transmembrane conductance receptor modulator therapy in cystic fibrosis, an update. Curr Opin Pediatr 2020;32(3):384–8.
49. Guimbellot JS, Taylor-Cousar JL. Combination CFTR modulator therapy in children and adults with cystic fibrosis. The Lancet Respir Med 2021;9(7):677–9.
50. Lehr CJ, Pilewski JM. Cystic fibrosis: candidate selection and impact of the cystic fibrosis transmembrane conductance regulator therapy. Curr Opin Organ Transpl 2022. https://doi.org/10.1097/MOT.0000000000000975.