Expectations about CFTR modulators among physicians from Italian Cystic fibrosis centers: a survey about the evolution of clinical practice paradigms for cystic fibrosis

Rosaria Casciaro[1], Stefano Costa[2], Mirco Ros[3], and Fabio Majo[4]

[1]Istituto Giannina Gaslini Istituto Pediatrico di Ricovero e Cura a Carattere Scientifico
[2]University of Messina
[3]Ospedale S. Maria di Ca' Foncello
[4]Bambino Gesù Children's Hospital

February 26, 2021

Abstract

CFTR modulators (CFTRm) were introduced recently but they are already profoundly changing Cystic Fibrosis (CF) landscape. This survey was conducted in 2018 to evaluate how their perception and use evolved in Italy, with focus on factors that could influence physician treatment decisions. Response rate was 75.6% and the majority of physicians (81%) had been working in CF for over 5 years. While traditional parameters such as lung function and nutritional status remain key evaluation criteria in relation to initiation and monitoring of CFTRm, pulmonary exacerbations ranked at least at the same level of importance in both pediatric and adolescent/adult patients homozygous for F508del, as well as those with residual function mutations. Increasing interest is shown for tools that can help detect early manifestations of disease such as Lung Clearance Index and imaging. Patient-related outcomes, such as ability to conduct daily activities, are also deemed relevant in decision to start and continue CFTRm. Physician decision to initiate treatment according to clinical presentation was similar in all groups, showing that more importance was given to severity/instability of disease rather than mutation type or age range. A relatively low percentage of physicians would treat asymptomatic patients, in particular very young or those with residual function mutations, showing reluctance to treat early in some patient groups in the absence of clear manifestations of CF. Increasing experience with CFTRm will allow to gain more long term evidence and will help shape new guidelines.

Title page

Expectations about CFTR modulators among physicians from Italian Cystic fibrosis centers: a survey about the evolution of clinical practice paradigms for cystic fibrosis

Rosaria Casciaro[a]; Stefano Costa[b]; Fabio Majo[c]; Mirco Ros[d]

[a]IRCCS G. Gaslini Institute, Genova, Italy ;[b]Gaetano Martino Hospital, Messina, Italy;[c] Cystic Fibrosis Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy; [d]Ca' Foncello Hospital, Treviso, Italy

Corresponding Author: Fabio Majo, IRCCS Bambino Gesù Children's Hospital, Piazza di Sant'Onofrio, 4, 00165 Rome, Italy; Email:*fabio.majo@opbg.net*; phone: +390668592045

Keywords

CFTR modulators; survey; monitoring; early intervention

Abbreviated title

Survey on CFTR modulators: Italian scenario

Abstract

CFTR modulators (CFTRm) were introduced recently but they are already profoundly changing Cystic Fibrosis (CF) landscape. This survey was conducted in 2018 to evaluate how their perception and use evolved in Italy, with focus on factors that could influence physician treatment decisions. Response rate was 75.6% and the majority of physicians (81%) had been working in CF for over 5 years. While traditional parameters such as lung function and nutritional status remain key evaluation criteria in relation to initiation and monitoring of CFTRm, pulmonary exacerbations ranked at least at the same level of importance in both pediatric and adolescent/adult patients homozygous for*F508del* , as well as those with residual function mutations. Increasing interest is shown for tools that can help detect early manifestations of disease such as Lung Clearance Index and imaging. Patient-related outcomes, such as ability to conduct daily activities, are also deemed relevant in decision to start and continue CFTRm. Physician decision to initiate treatment according to clinical presentation was similar in all groups, showing that more importance was given to severity/instability of disease rather than mutation type or age range. A relatively low percentage of physicians would treat asymptomatic patients, in particular very young or those with residual function mutations, showing reluctance to treat early in some patient groups in the absence of clear manifestations of CF. Increasing experience with CFTRm will allow to gain more long term evidence and will help shape new guidelines.

Introduction

This millennium saw a transformation in the way cystic fibrosis (CF), a lethal, autosomal recessive disease affecting over 80,000 people worldwide[1], is treated. This monogenic disease is caused by mutations in the *cystic fibrosis transmembrane conductance regulator (CFTR)* gene[2,3]. The altered function of the CFTR protein that is present in multiple epithelia such as the lung, pancreas, gastrointestinal tract, liver, and reproductive tract[4,5] causes abnormal viscous secretions and in the airways in particular, chronic infection and exuberant inflammatory response leading to progressive respiratory failure and death if patient cannot get access to a lung transplant[6]. Historically, treatment of CF has involved symptomatic treatment aiming at increasing mucociliary clearing, preventing infection and inflammation as well as nutritional therapies[7-9]. Change of treatment paradigm started in 2012, with the availability of the first therapy targeting the CFTR protein basic defect on a small minority of the population carrying at least one gating mutation[10,11]. This new class of drugs called CFTR modulators (CFTRm) rapidly increased with the addition of new combinations targeting additional CF patient groups, ivacaftor/lumacaftor, ivacaftor/tezacaftor and more recently ivacaftor/tezacaftor/elexacaftor, each of them approved for use in patients with specific genotypes[12]. Although genotype does not fully correlate with phenotype, patients homozygous for*F508del* , the most frequently represented mutation worldwide, generally have a rapidly progressive disease while patients with mutations associated with residual function of the CFTR protein tend to have a slower course of disease[13]. With the increasing availability of compounds addressing the cause of the disease, the possibility to change the course of CF is now within reach and there are high hopes in the community to transform this rapidly lethal disease into a chronic disease. While longer follow up is needed to fully understand the potential of this new class of drugs, treatment decisions can be influenced by the length of personal experience with CFTR modulators, expectations in the longer term and the perception of specific burden of illness by subgroups of mutation types or age range. We conducted this survey among Italian CF physicians to understand their perception and use of CFTRm, checking their treatment preference and opinion on how early treatment should be started in different patient groups with different disease expression. This is the second survey conducted by our group, at 3 year interval from the previous one performed using the same modalities[14].

Materials and methods

Participation to the survey was proposed through an online platform to all physicians from Italian CF centers and was voluntary and anonymous. No IRB approval was required considering the study type. Questionnaire was composed of 16 item including 3 profiling questions. The questionnaire focused on the three groups

of patients for whom CFTR modulators were authorized at the time: *F508del* homozygous patients below and above 12 years of age and patients with RF mutations. Questions explored expectations of efficacy of CFTRm, criteria used to start therapy, monitoring parameters, treatment preferences according to disease stage and treatment preference in *F508del* homozygous patients. A Likert scale in 4 points (not at all, slightly, somewhat, a lot) was used to rank the answers. Descriptive statistical analysis was performed to depict the distribution of answers. CHI-squared test was used to investigate a possible center effect influencing the answers (clusterization) a statistical significance was considered when p-value was <0.05. Cohen's kappa coefficient (κ) was calculated to evaluate possible correlation between different answers, considering$k$ =1 as complete concordance.

Results

The survey was conducted between May 3rd and October 2nd 2018. Of the 78 clinicians contacted, 59 (75.6%) answered the questionnaire; the 59 clinicians participating to the survey were representative of 29 of the 31 CF centres in Italy. 48 participating physicians (81%) had been working in the field of CF for over 5 years, including 31 clinicians (53%) who had over 11 years or experience. The majority of respondents (76%) works in mixed (pediatric and adult) CF centres, and 51% follow >200 CF patients. Of note, respondents answered 100% of questions. The full list of questions is presented in Table 1.

Clinicians expectations about CFTR modulator therapy

The vast majority of clinicians declared to expect moderate to great improvements in lung disease (88%), nutritional status (90%), ability to perform activities of daily living (86%) and survival (76%) but none or slight effect on exocrine pancreatic sufficiency (71%), endocrine pancreatic function (71%) and liver disease (78%). More specifically, clinicians expect moderate to great improvement on the number of exacerbations (95%) and slowing down of annual decline in FEV1 (86%) but none or slight increase in FEV1 (63%) and little or no improvement of pulmonary imaging (59%).

Criteria used to start and monitor CFTR modulator therapy

Table 2 presents the distribution of responses on criteria used to start CFTRm therapy. The number of exacerbations is perceived by respondents as the most useful parameter to decide to start the therapy with CFTR modulators: this parameter is deemed "somewhat useful" to "very useful" by 95% of respondents for *F508del* -homozygous pediatric patients, by 97% for *F508de* l-homozygous adult patients and by 90% for patients with residual function. Following respiratory outcomes, BMI z-score and ability to perform activities of daily living are also considered useful parameters in F508del-homozygous pediatric ("somewhat useful" to "very useful" in 95% and 80% of respondents, respectively) and adult patients ("somewhat useful" to "very useful" in 95% and 90% of respondents, respectively) and in patients with residual function ("somewhat useful" to "very useful" in 86% and 80% of respondents, respectively). Bacterial colonization is deemed somewhat to very helpful for 56-68% of respondents (highest percentage in young homozygous patients). Of note, only exacerbations get close to 50% of opinions of high usefulness (very useful 41-51%). The same parameters are deemed useful to monitor CFTRm therapy and in similar proportions, although growth percentiles and Lung clearance index (LCI) are considered somewhat more important for young*F508del* -homozygous patients (Table 3). Lung imaging was also deemed useful in all groups for both initiation and monitoring of therapy (68-75% somewhat/very useful). In addition, sweat chloride is considered somewhat to very useful for about 75% of physicians in all groups of patients.

CFTRm use according to disease stage and selection of CFTRm indicated in same patient group

Table 4 shows the distribution of responses on CFTRm use by disease stage and patient groups (percentage of physicians who would consider use in all patients). Systematic use in asymptomatic patients would be considered in 19, 27 and 17% of pediatric *F508del* homozygous, adult *F508del* homozygous and patients with residual function mutations, respectively while 54 to 58% of respondents would evaluate CFTRm use case by case (data not shown). Favorable opinion of use in all patients increases with severity of clinical

presentation with 53-56% positive responses for mild disease stage, 69-78% in case of fully expressed stable disease and 90-92% for fully expressed disease with worsening symptoms. About half of respondents would consider CFTRm in terminal disease stage in patients >12 years *F508del*homozygous and RF while most physicians would evaluate use case by case for non adherent patients (data not shown). Half of respondents (51%) would choose to use tezacaftor/ivacaftor association to start CFTR modulator therapy in *F508del* homozygous patients compared to 17% who would start with lumacaftor/ivacaftor. The main very important reasons to start with lumacaftor/ivacaftor were clinical experience (60%) and safety profile (80%) while strong motivation for starting with tezacaftor/ivacaftor was based on expectation of efficacy for 53% of health care professionals. No significant center-effect or correlation between answers was found.

Discussion

Cystic fibrosis landscape is expected to change significantly over the next years. The place in CF therapy of each CFTRm by indication is still to be fully understood, especially with regards to expected long term effects and potential benefits of early intervention, in particular in very young patients. Physicians opinion will predictably evolve as more real world data are being collected and with increasing experience. We undertook this survey to see how clinical use of CFTRm changed over time with their increasing availability in Italy. Ivacaftor and lumacaftor/ivacaftor were the only CFTRm available at the time of our study, the latter available for *F508del* homozygous patients above 12 years of age at the time of the first survey conducted in 2015, its indication extended to younger ages at the time of the 2018 survey. No drug was available for patients with residual function mutations until 2018, however tezacaftor/ivacaftor phase III data on both patients homozygous for *F508del* mutation and those carrying a residual function mutation had already been published in the scientific literature. Considering that these new indications or extensions introduced the use of CFTRm in new patient groups, we designed the questionnaire to explore physicians attitude in *F508del*homozygous patients aged 12 years and above as an historical group compared to younger *F508del* homozygous patients and those with residual function mutations. Reaching out to all CF physicians was facilitated by the centralization of care in CF centers evenly distributed on the national territory. Response rate of 76% was satisfactory and similar to that of previous survey[14], showing the willingness of Italian health care professionals to share their experience and allowing to consider the outcome as representative of the general opinion in Italy. Of note, most respondents had significant experience in the field of CF, with at least 5 years of work in a CF center. A general overview of responses to the different questions shows that traditional parameters such as lung function and nutrition status remain key evaluation criteria in relation to initiation and monitoring of CFTRm in all groups and physicians expect to observe improvement, consistently with clinical trial results. Nutritional status is considered a fundamental parameter in relation to initiation of CFTRm across all the different patient groups and growth percentiles is considered a useful parameter to monitor in pediatric patients. This is in line with literature data showing that improvement of nutritional status is directly linked with increased survival in CF patients. With regard to pulmonary outcomes, it should be underlined that more than FEV1, the number of exacerbations is considered particularly relevant in all groups for both initiation and monitoring of therapy. This is consistent with the expected deleterious effect of increasing number of exacerbations on FEV1 decline and survival. We also observed interest in measuring exercise tolerance and patient related outcomes such as ability to conduct daily activities as well as in tools that can help detect early manifestations of disease such as LCI and imaging. LCI was deemed particularly relevant in the younger age group, with 36% of physicians who judged this test very useful in*F508del* homozygous patients under 12 years of age. Imaging can also be useful in all patient groups to identify early lung damage and as such, was viewed as useful by clinicians for initiation and monitoring of CFTRm therapy. For follow up in particular, imaging can provide objective signs of the effects of CFTRm on lung parenchyma. A few studies report CT scan parameters combined through a scoring system as exploratory endpoints. In particular, reduction of mucus plugging, bronchiectasis[15,16] and airway wall thickness[17] were observed after one year of treatment with ivacaftor, while improvement of bronchiectasis and air trapping were seen after 6 months of lumacaftor/ivacaftor treatment[18]. Limitations related to cumulative exposure to ionizing radiation might be overcome by tools such as Magnetic Resonance Imaging that look promising for closer monitoring of the effect of CFTRm[19]. Relatively little emphasis

was given to pancreatic function, but this is consistent with the start of CFTRm (at the time of conduct of the survey) at an age deemed too old to expect great impact. Encouraging data on modification of biological markers with younger age of CFTRm start raises some hopes on possibility of changing pancreas exocrine function status with very early intervention with this class of drugs[20]. Sweat chloride measurement was also mentioned as useful monitoring tool and it is likely used by physicians to estimate adherence. When asked about treatment initiation according to clinical presentation and disease stage, health care professionals provided similar responses in homozygous *F508del* patients under or over 12 years of age and residual function patients as well, showing that severity/instability of disease prevails on this decision and is not influenced by mutation type or age range. A relatively small proportion of physicians would treat systematically asymptomatic patients with less than 20% for younger*F508del* homozygous patients or those with residual function mutations and somewhat more (27%) for *F508del* homozygous over 12 years of age. Intention to initiate treatment increases considerably (over 50% in all groups) when patients show light manifestations of disease. Further explorations of what is meant by light manifestations would be interesting to understand biomarkers of interest to detect initial organ damage before symptoms occur. Willingness to initiate CFTRm treatment reaches 69-78% in case of fully expressed disease and exceeds 90% in patients with worsening disease. Interestingly, compared to survey conducted in 2015[13], intention to initiate CFTRm treatment in *F508del* homozygous over 12 years of age increased by 8-11% in all severity categories and even doubled for patients in terminal stage, showing increasing confidence of physicians with increasing experience of CFTRm. Nevertheless, some concern on initiating CFTRm in asymptomatic pediatric patients actually exists and this might be related to lack of long term experience of CFTRm in pediatric CF patients. This is in contrast with general belief in early intervention which is at the basis of CF care with all efforts made to intervene as soon as possible once diagnosis of disease is made, in order to warrant optimal long term outcomes. Continued observation will help us understand the magnitude of long term impact of early use of CFTRm. For now, simulation models can be used to predict long term effects, showing increased survival up to 23.4 years in pediatric CF patients treated early with lumacaftor/ivacaftor[21]. Registry data will allow documentation of effect of CFTRm on hard outcomes such as mortality and transplant, already shown for ivacaftor[22]. Limitations of this study are inherent to surveys based on voluntary participation, however high response rate allows to consider the sample as representative of the opinion in the Italian CF community. Survey can be conducted quickly and can inform how health care professional opinion is formed as new tools are made available and this could be of particular value in a rare disease field. We are not aware of any other published survey similar to ours.

In conclusion, the introduction of CFTRm in the therapeutic armamentarium is progressively changing treatment protocols in CF. Early intervention with drugs that act on the causal mechanism of disease have the potential to change the progression of disease, stimulating some physicians to start treatment regardless of symptoms. Our survey shows that CF HCPs have high expectations on CFTRm effectiveness. Pulmonary exacerbations represent the most important outcome to consider in CF patient both for start a CFTRm and as a monitoring parameter. This is consistent with the attitude of physicians to consider CFTRm treatment according to disease stage, considering more severe disease or non stable disease as priorities. On the other hand, there is increasing interest in parameters such as imaging and above all LCI as useful tools in order to predict disease progression in asymptomatic and/or pediatric patients. It is arguable that with increased experience with CFTRm and with new insight into the understanding of disease progression the attitude towards early intervention could become more prominent. Treatment scenario is rapidly changing and will call for revision of current guidelines.

Acknowledgements

Authors received fees from Vertex Pharmaceuticals (Italy) srl to conduct the survey described in this manuscript. Methodological support, project coordination and logistical support were provided to the authors by Editamed which received funding from Vertex Pharmaceuticals (Italy) srl.

References

1. Lubamba B, Dhooghe B, Noel S, Leal T. Cystic fibrosis: Insight into CFTR pathophysiology and

pharmacotherapy. Clin Biochem. 2012;45:1132–1144.
2. Boucher RC. An overview of the pathogenesis of cystic fibrosis lung disease. Adv Drug Deliv Rev. 2002;54:1359–1371.
3. Ong T, Ramsey BW. New therapeutic approaches to modulate and correct cystic fibrosis transmembrane conductance regulator. Pediatr Clin North Am. 2016; 63:751–764.
4. Davies JC, Alton EW, Bush A. Cystic fibrosis. Br Med J. 2007; 335(7632):1255–1259.
5. Spoonhower KA, Davis PB. Epidemiology of cystic fibrosis. Clin Chest Med. 2016;37:1–8.
6. Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. N. Engl J Med. 2005;352(19):1992-2001
7. Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, Accurso FJ. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr. 2009;155(Suppl. 6):S73–S93.
8. Lahiri T, Hempstead SE, Brady C, Cannon CL, Clark K, Condren ME, Davis SD. Clinical practice guidelines from the Cystic Fibrosis Foundation for preschoolers with cystic fibrosis. Pediatrics. 2016;137:1–26.
9. Edmondson C, Davies JC. Current and future treatment options for cystic fibrosis lung disease: Latest evidence and clinical implications. Ther Adv Chronic Dis 2016;7:170–183
10. Pettit RS, Fellner C. CFTR modulators for the treatment of cystic fibrosis. PT. 2014;39:500–511.
11. Guimbellot J, Sharma J, Rowe SM. Toward inclusive therapy with CFTR modulators: Progress and challenges. Pediatr Pulmonol. 2017;52(S48):S4–S14.
12. Gramegna A, Contarini M, Aliberti S, Casciaro R, Blasi F, Castellani C. From Ivacaftor to Triple Combination: A Systematic Review of Efficacy and Safety of CFTR Modulators in People with Cystic Fibrosis. Int J Mol Sci. 2020; 21(16): 5882.
13. Salvatore D, Padoan R, Buzzetti R, Amato A, Giordani B, Ferrari G, Majo F. Patients with cystic fibrosis having a residual function mutation: Data from the Italian registry. Pediatr Pulmonol. 2019;54(2):150-157.
14. Casciaro R, Costa S, Dang P, Majo F, Ros M. Lumacaftor/ivacaftor combination therapy for cystic fibrosis: A nationwide survey among clinicians. Clin Respir J. 2018 Apr;12(4):1767-1768
15. Hisert KB, Heltshe SL, Pope C, Jorth P, Wu X, Edwards RM, Radey M, Accurso FJ, Wolter DJ, Cooke G, et al. Restoring Cystic Fibrosis Transmembrane Conductance Regulator Function Reduces Airway Bacteria and Inflammation in People with Cystic Fibrosis and Chronic Lung Infections. Am J Respir Crit Care Med. 2017;195(12):1617-1628.
16. Ronan N, Einarsson GG, Twomey M, Mooney D, Mullane D, NiChroinin M, O'Callaghan G, Shanahan F, Murphy DM, O'Connor OJ, et al. CORK Study in Cystic Fibrosis: Sustained Improvements in Ultra-Low-Dose Chest CT Scores After CFTR Modulation With Ivacaftor. Chest. 2018;153(2):395-403.
17. Sheikh SI, Long FR, McCoy KS, Johnson T, Ryan-Wenger NA, Hayes D Jr. Computed tomography correlates with improvement with ivacaftor in cystic fibrosis patients with G551D mutation J Cyst Fibros. 2015 Jan;14(1):84-9.
18. Brody A, Nagle S, Hug C, Marigowda G, Waltz D, Goldin J, Ratjen F, Wang L. S93 Effect of lumacaftor/ivacaftor on total, bronchiectasis, and air trapping computed tomography (ct) scores in children homozygous for *f508del-cftr* : exploratory imaging substudy. Thorax. 2017;72:A57.
19. Altes TA, Johnson M, Fidler M, Botfield M, Tustison NJ, Leiva-Salinas C, de Lange EE, Froh D, Mugler JP 3rd. Use of hyperpolarized helium-3 MRI to assess response to ivacaftor treatment in patients with cystic fibrosis J Cyst Fibros. 2017;16(2):267-274.
20. Davies JC, Wainwright CE, Sawicki GS, Higgins MN, Campbell D, Harris C, Panorchan P, Haseltine E, Tian S, Rosenfeld M. Ivacaftor in infants aged 4 to <12 months with cystic fibrosis and a gating mutation: Results of a 2-part Phase 3 clinical trial. Am J Respir Crit Care Med. 2020 Oct 7. doi: 10.1164/rccm.202008-3177OC.
21. Rubin JL, O'Callaghan L, Pelligra C, Konstan MW, Ward A, Ishak JK, Chandler C, Liou TG. Modeling long-term health outcomes of patients with cystic fibrosis homozygous for F508del-CFTR treated with lumacaftor/ivacaftor. Ther Adv Respir Dis. 2019;13:1753466618820186.

22. Bessonova L, Volkova N, Higgins M, Bengtsson L, Tian S, Simard C, Konstan MW, Sawicki GS, Sewall A, Nyangoma S, et al. Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor. Thorax. 2018;73(8):731-740

Hosted file

`tables.pdf` available at https://authorea.com/users/398352/articles/510987-expectations-about-cftr-modulators-among-physicians-from-italian-cystic-fibrosis-centers-a-survey-about-the-evolution-of-clinical-practice-paradigms-for-cystic-fibrosis