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ORIGINAL ARTICLE: CYSTIC FIBROSIS—PEDIATRIC & ADULT

Patients eligible for modulator drugs: Data from cystic fibrosis registry of Turkey

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Abstract

Background: A better understanding of cystic fibrosis transmembrane conductance regulator biology has led to the development of modulator drugs such as ivacaftor, lumacaftor-ivacaftor, tezacaftor-ivacaftor, and elexacaftor-tezacaftor-ivacaftor. This cross-sectional study evaluated cystic fibrosis (CF) patients eligible for modulator drugs.

Methods: Data for age and genetic mutations from the Cystic Fibrosis Registry of Turkey collected in 2018 were used to find out the number of patients who are eligible for modulator therapy.

Results: Of registered 1488 CF patients, genetic analysis was done for 1351. The numbers and percentages of patients and names of the drugs, that the patients are eligible for, are as follows: 122 (9.03%) for ivacaftor, 156 (11.54%) for lumacaftor-ivacaftor, 163 (11.23%) for tezacaftor-ivacaftor, and 57 (4.21%) for elexacaftor-tezacaftor-ivacaftor. Among 1351 genotyped patients total of 313 (23.16%) patients are eligible for currently licensed modulator therapies (55 patients were shared by ivacaftor and tezacaftor-ivacaftor, 108 patients were shared by lumacaftor-ivacaftor and tezacaftor-ivacaftor, and 22 patients were shared by tezacaftor-ivacaftor and elexacaftor-tezacaftor-ivacaftor groups).

Conclusions: The present study shows that approximately one-fourth of the registered CF patients in Turkey are eligible for modulator drugs. As, frequent mutations that CF patients have in Turkey are different from North American and European CF patients, developing modulator drugs effective for those mutations is necessary. Furthermore, as modulator drugs are very expensive currently, financial support of the government in developing countries like Turkey is noteworthy.

KEYWORDS
cystic fibrosis, modulator drugs, national registry

1 | INTRODUCTION

Cystic fibrosis (CF) is a progressive, life-shortening and -threatening genetic multiorgan disease caused by a loss of cystic fibrosis transmembrane conductance regulator (CFTR) protein quantity and/or function due to mutations in the CFTR gene.[1] CFTR modulators (read-through agents, correctors, potentiators, stabilizers and amplifiers) are a class of drugs which directly target the defective CFTR protein, improve its function and result in clinical improvements in CF patients.[2]

Unfortunately modulator drugs are confined to people with a limited selection of genetic mutations. In Turkey a very limited number of patients are able to use modulator drugs because, currently, those drugs are not covered by government-sponsored health insurance.

In this study, we evaluated CF patients recorded in the Cystic Fibrosis Registry of Turkey who is eligible for modulator drugs.

2 | METHODS

The CF Registry of Turkey was established by the "Turkish Pediatric Respiratory Diseases and Cystic Fibrosis Society" and first demographic and annually reported data, consisted of 15 and 79 variables, respectively, from the national registry was reported recently except modulator therapy eligibility of patients.[3] This cross-sectional study was conducted using data in terms of age and genetic mutations from the Cystic Fibrosis Registry of Turkey collected in 2018 to find out (a) the total amount of patients who

are eligible for modulator therapy, (b) the number of patients qualified for specific CFTR modulators.

The establishment of the national registry and data input was approved by the local ethics committee (Hacettepe University Ethics Board, reference numbers: HEK 07/16-21 and GO 18/473-31). Informed consent was obtained from all patients/parents.

The decision of eligibility for modulator drugs was made according to the current approval status: *lumacaftor-ivacaftor:* aged more than equal to 2 years that have two copies of the F508del mutation; *tezacaftor-ivacaftor:* aged more than equal to 6 years that have two copies of the F508del mutation or a single copy of one of 26 specific mutations (A455E, A1067T, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K, F1052V, F1074L, K1060T, L206W, P67L, R74W, R117C, R347H, R352Q, R1070W, S945L, S977F, 711 + 3 A→G, 2789 + 5G→A, 3272-26A→G, 3849 + 10kbC→T, E831X); *ivacaftor:* aged more than equal to 6 months that have a single copy of one of the mutations approved for tezacaftor-ivacaftor or 12 other specific mutations (G178R, G551D, G551S, G1069R, G1244E, G1349D, R117H, R1070Q, S549N, S549R, S1251N, S1255P); *elexacaftor-tezacaftor-ivacaftor:* aged more than equal to 12 years that have a single copy or two copies of the F508del mutation.

As our outcome was numbers and percentages of patients, and names of the drugs that the patients are eligible for, counts and percentages were reported for categorical variables.

3 | RESULTS

There were 1488 patients registered from 23 centers. Genetic analysis was done for 1351 patients between ages 6 months and 43 years. Genetic testing used by the centers was not standardized; some centers used small panels and some centers used full sequencing; even some patients had small panels first and then full sequencing.

Two mutations were identified in 892 (66%) patients, one mutation was identified in 201 patients (14.9%), and no mutations could be found in 258 (19.1%) patients.

Among 1985 alleles where a mutation was detected, the most common mutation was F508del in 539 alleles (27.15%); 220 patients had a single copy and 159 patients had two copies of the F508del mutation. Allelic frequencies of the most common mutations that were more than equal to 1% presented in Table 1.

Of 159 patients homozygous for F508del, 156 were more than equal to 2-year-old, 108 were more than equal to 6-year-old and 57 were more than equal to 12-year-old.

According to the criteria and current approval status for CF patients mentioned in methods section, numbers and percentages of patients and names of the drugs, that the patients are eligible for, are as follows: 122 (9.03%) for ivacaftor, 156 (11.54%) for lumacaftor-ivacaftor, 163 (11.23%) for tezacaftor-ivacaftor, and 57 (4.21%) for elexacaftor-tezacaftor-ivacaftor. Among 1351 genotyped patients total of 313 (23.16%) patients are eligible for currently licensed modulator therapies (55 patients were shared by ivacaftor and tezacaftor-ivacaftor, 108 patients were shared by lumacaftor-ivacaftor and tezacaftor-ivacaftor, and 22 patients were shared by tezacaftor-ivacaftor and elexacaftor-tezacaftor-ivacaftor groups) (Figure 1).

TABLE 1 Allelic frequencies of the most common mutations

Mutation name	Number of alleles	Allelic frequency (%)
F508del	539	27.1
G542X	97	4.7
1677delTA	83	4
N1303K	77	3.7
2183AA→G	75	3.6
G85E	73	3.5
2789 + 5 G>A	68	3.3
E92K	50	2.4
W1282X	32	1.5
R347P	31	1.5
D110H	28	1.3
M470V	28	1.3
D1152H	26	1.2
L997F	26	1.2
V470M	26	1.2
F1052V	22	1

4 | DISCUSSION

The present study shows that approximately one-fourth of registered CF patients in Turkey are eligible for modulator drugs.

There has been encouraging progress in the development of CFTR modulators. The first introduced CFTR modulator was ivacaftor, a potentiator, which is effective for CF patients carrying the G551D mutations, and in 2012 ivacaftor became available to those patients. However, as only approximately 4% to 5% of patients with CF have the G551D mutation on at least one allele,[5,6] studies evaluating the effect of ivacaftor for non-G551D mutations has emerged.[7,8] Among CF patients recorded in the Cystic Fibrosis Registry of Turkey, although none of them has G551D mutation, 122 (9.03%) are eligible for ivacaftor.

Whether the use of ivacaftor could be expanded to include the F508del, the most common CFTR mutation,[9] was also investigated, but ivacaftor did not improve lung function,[10] indicating that a potentiator alone is not enough to rescue this mutant protein. Thus, lumacaftor, a corrector, combined with ivacaftor; lumacaftor-ivacaftor combination is available for patients aged more than equal to 12 years that are homozygous for the F508del mutation after July 2015.[11] Lumacaftor-ivacaftor regimen was associated with clinically meaningful reductions in pulmonary exacerbation rate, improved

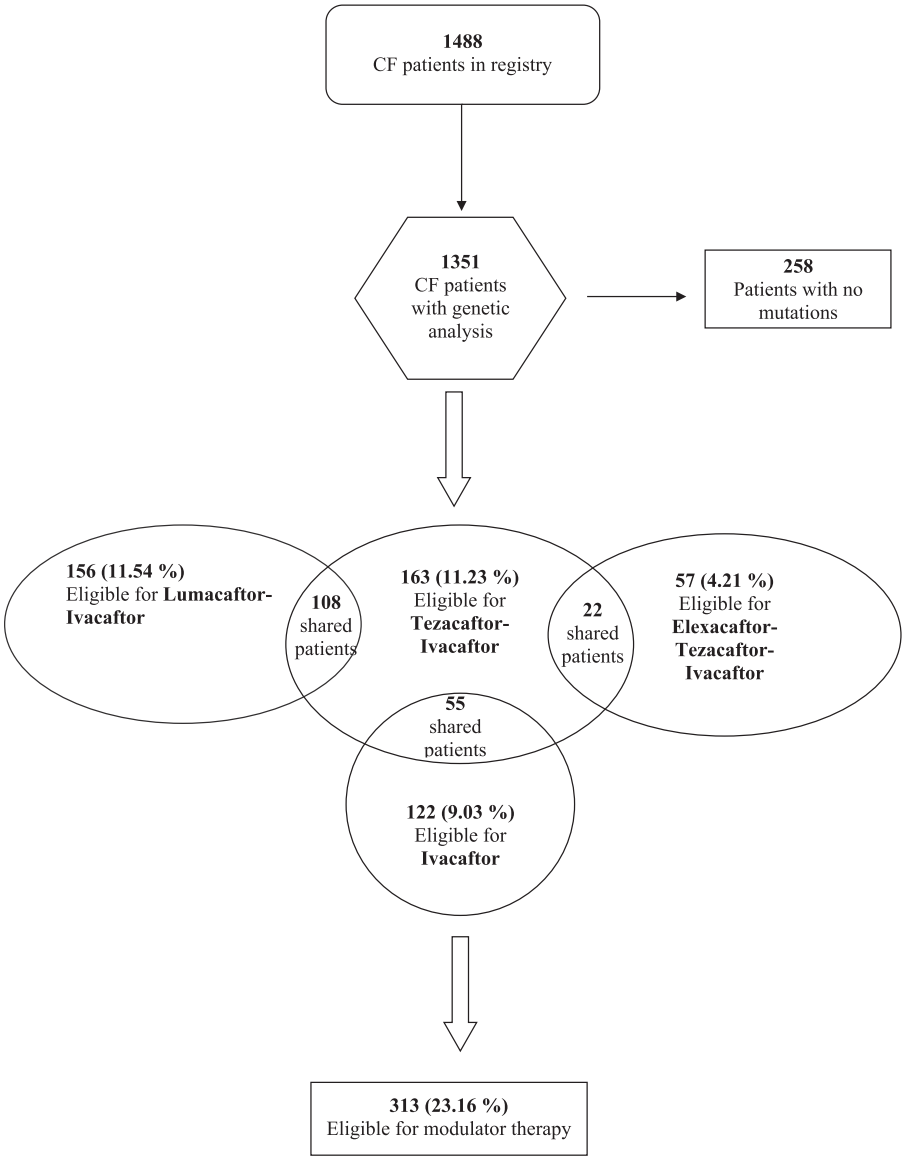

FIGURE 1 Summary of the patients eligible for modulator therapy who were recorded in the Cystic Fibrosis Registry of Turkey

BMI, and lung function.[11] According to the results of this study, 156 (11.54%) CF patients are eligible for lumacaftor-ivacaftor therapy in Turkey.

Tezacaftor, another small-molecule corrector, in combination with ivacaftor revealed significant treatment effects in terms of pulmonary functions and quality of life for patients heterozygous for the F508del and a CFTR residual function mutation.[12] Our registry-based analysis revealed that 47 (3.47%) patients are eligible for tezacaftor-ivacaftor therapy.

Although the combination of a single corrector, either lumacaftor or tezacaftor, with the potentiator ivacaftor improves clinical outcomes, including lung function and the rate of pulmonary exacerbations,[11,12] neither of these dual combinations is sufficiently effective in patients with CF who have a single F508del allele. A next-generation corrector elexacaftor combined with tezacaftor and ivacaftor to treat those patients. Recent studies reported that elexacaftor-tezacaftor-ivacaftor, a triple-combination CFTR modulator regimen, is efficacious in patients with CF with F508del–minimal function genotypes, in whom previous CFTR modulator regimens were ineffective.[13-15] According to our registry, 57 (4.21%) patients among 1351 patients are eligible for elexacaftor-tezacaftor-ivacaftor modulator regimen in Turkey.

Sawicki et al[16] reported that ivacaftor was prescribed to 64% of eligible United States patients within the first 6 months after Food and Drug Administration approval; nearly 80% have prescribed this therapy within 1 year. In their following study, Sawicki et al[17] observed a lower rate of use of lumacaftor-ivacaftor in the F508del homozygous US CF population aged more than equal to 12 years (40% within 6 months and 54% within a year), with clinical, socioeconomic, and regional differences potentially impacting clinical use of this therapy in eligible populations. In Turkey, none of the patients is able to use modulator drugs because, currently, those drugs are not covered by government-sponsored health insurance.

For our CF patients, there are three important points to look through. First of all, as genetic testing used by the centers was not standardized, some of the registered patients could not be tested for CFTR mutations and no mutations could be found in 19% of the patients; this is an important limitation for detecting patients' eligibility for modulator drugs. Second, among the 16 most common mutations shown in Table 1, only the patients carrying D110H and 2789 + 5G>A mutations are eligible for modulator drugs, therefore, studies evaluating the effectiveness of the modulator drugs among those patients carrying other frequent mutations are needed. And finally, modulator drugs are very expensive currently and there is no financial support of the government to buy them.

In conclusion, the present study shows that approximately one-fourth of the registered CF patients in Turkey are eligible for modulator drugs. As frequent mutations that CF patients have in Turkey are different from North American and European CF patients, developing modulator drugs effective for those mutations is necessary. Furthermore, modulator drugs are very expensive currently and patients can't afford to buy them; therefore, financial support of the government in developing countries like Turkey is noteworthy for CF patients.

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