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Evaluating The Real-World Effectiveness of A New Class of Drugs For Cystic Fibrosis: A Study Based On European Cystic Fibrosis Society Patient Registry Data

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INTRODUCTION

Cystic fibrosis (CF) is a heterogeneous multisystemic disease. Despite considerable improvement in survival, CF remains a life-shortening disease with respiratory failure as the main cause of death. In 2020, elexacaftor/tezacaftor/ivacaftor (ETI) became available as a new highly effective CFTR-modulator therapy targeting the basic protein defect for people with a specific gene variant, and it was shown to improve lung function respiratory symptoms, and other clinical outcomes, including pulmonary exacerbations (PEx) [1]. However, despite the reduced frequency of PEx, these events remain an important driver of morbidity and mortality in people with CF (pwCF) [2]: in 2023, 16% of adults with CF in Europe experienced at least one PEx during the year [3]. The full extent of CFTR modulators effect on chronic airway infections and the recurrent PEx, especially in the long-term, remains uncertain with some studies reporting inconsistent results [4].

OBJECTIVES

This study aimed to evaluate the real-world effectiveness of ETI therapy on PEx frequency in pwCF followed up between 2018 and 2023, using data from the European Cystic Fibrosis Society Patient Registry (ECFSPR). Specifically, a longitudinal comparison was conducted to evaluate the effectiveness of the new CFTR-modulator therapy on the number of PEx and the prevalence of chronic infections over time.

METHODS

Data were obtained from the ECFSPR, a population-based Registry that collects clinical and demographic data on an annual basis according to agreed definitions of a common set of variables from Centres and national Registries in Europe and neighbouring countries from 2008 to 2023 [9].

To determine the effectiveness of ETI on PEx and chronic infections, a retrospective and longitudinal comparison from 2018 to 2023 was implemented. The analysis included the following variables: total number of days of intravenous antibiotics (IV Abx), including those performed both in hospital and at home (as a proxy for PEx), number of days of IV Abx performed exclusively in hospital, total number of days in hospital for any cause and the presence of chronic infections, including Pseudomonas aeruginosa, Burkholderia Cepacia Complex and Staphylococcus aureus. The first three variables were analysed both as continuous and as categorical (≥1 day vs. 0 days). The chronic infections were instead categorized as the presence of at least one infection versus no infection. To assess whether there were significant differences between the paired periods before and after treatment, the Wilcoxon signed-rank test and McNemar's test for paired data were used, as the same pwCF were evaluated at two time points.

All analyses were performed using R software.

RESULTS

The study included pwCF aged 12-60 years; pwCF who underwent solid organ transplants were excluded. Partici-

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pants had either an F508del homozygous genotype or were F508del heterozygous with a minimal function variant The analyses were restricted to those who started ETI modulator therapy in 2020 (N= 6,628). Only people with available data on the number of days on IV Abx therapy administered at home and in hospital were considered, resulting in a final study population of 4,602 pwCF.

Comparison of two years before and two years after starting ETI showed that the percentage of pwCF with at least one day on IV Abx decreased significantly from 64% to 23% ($p<0.001$), the percentage of pwCF with at least one day on IV Abx in hospital decreased from 50% to 16% ($p<0.001$) and, in parallel, that the percentage of pwCF hospitalized dropped from 56% to 24% ($p<0.001$). Also considering the corresponding variables as continuous, all the differences remain statistically significant. Notably, these improvements measured by total days on IV antibiotics and related variables persisted through three years post-ETI initiation.

The prevalence of at least one chronic infection significantly decreased from 67.8% to 36.8% after 2 years of ETI therapy ($p<0.001$). Number of chronic infections further decreased to 34.5% after 3 years of treatment.

CONCLUSIONS

This analysis of the ECFSPR data demonstrates a marked reduction in PEx after the introduction of the new highly effective CFTR-modulator therapy. The introduction of ETI significantly reduced the clinical burden in pwCF, with decreases of days on IV Abx, hospitalizations and chronic infections. These benefits were observed consistently after 3 years of therapy.

Further steps will include the implementation of statistical models to study changes in days on IV Abx as well as in other clinical outcomes before and after ETI.

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