WS13.2

The Swedish cystic fibrosis Registry facilitates the evaluation of Orkambi® treatment

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Objectives: Starting July 1, 2018, the Dental and Pharmaceutical Benefits Agency decided that Orkambi® was to be subsidized by the Swedish state. The decision was accompanied by the following restrictions: 1. Treatment initiated at a CF Centre with close follow-up of effect and adverse events 2. Set treatment goals evaluated after one year 3. Follow-up via the Swedish CF Registry.
The aim was to investigate whether the registry could facilitate the evaluation of Orkambi® treatment.
Methods: A national follow-up program for the first year of Orkambi® treatment was established by The Swedish CF Working Group. Extra fields were added to the registry to fit the program and staff was hired to ensure that data was entered correctly. Mandatory check-ups were at treatment start and after 1, 3, 6, 9 and 12 months.
Results: The registry is used by all 4 centres and all patients that initiated Orkambi® are included in the follow-up program. Up to July 31, 2019, 190 patients entered the program. 25 (13%) patients stopped treatment due to adverse events. Mean age (SD) at start was 22.9 (12.7) yrs with FEV1pp of 77 (22)% and LCI (< 18 yrs) 8.89 (1.99). BMI in adults was 21.9 (2.51) and BMI z-score in children −0.35 (0.82).
87 patients (35 children) had been on treatment for >6 months July 31, 2019. The sweat test decreased in average 18 mmol/l (range −48 to +14 mmol/l) after 3 months. After 6 months, FEV1 showed a trend of improvement in the adult population while it was stable in the paediatric population (6–18 yrs) where a decrease of LCI (0.7 units) was seen. Both BMI and BMI z-score showed a slight increase. Comparing the 180 days before starting Orkambi® to the180 days after treatment start, the mean number of days on iv antibiotics per patient decreased from 7.2 to 3.1 days.
Conclusions: The follow-up program for Orkambi® shows that the Swedish CF-registry is a useful tool for evaluation of new therapies. Longer follow-up time will be presented in June 2020.

WS13.3

Tobacco smoke exposure limits the benefit of Symdeko® in paediatric cystic fibrosis patients: Cystic Fibrosis Foundation Patient Registry analysis

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Objectives: Tobacco smoke exposure reduces CFTR functional expression *in vitro* and contributes to acquired CFTR dysfunction in animal models. We investigated whether smoke exposure inhibits the clinical benefit of CFTR modulators, focusing on tezacaftor/ivacaftor (SYMDEKO®), FDA-approved in February 2018 for F508del homozygous patients age 12 years and older.
Methods: A retrospective analysis of data in the CF Foundation Patient Registry (CFFPR, 2016–2018) compared change in lung function (GLI FEV_1%) after SYMDEKO® initiation in smoke-exposed vs unexposed patients age 12–18 years. Smoke exposure was dichotomized based on annual self-report. Its impact was assessed with fixed-effects modelling, which accounts for non-time-varying factors (sex, race, parent education) and additionally controlled for time-varying covariates.
Results: SYMDEKO® was prescribed to 1,429 patients: mean age 14.7 (SD 0.07) years, 54.6% female, mean baseline FEV_1% 83.3 (0.51), 27.6% smoke-exposed. During the study period, FEV_1% improved 0.25% (95% CI: −0.39, 0.89) in those on SYMDEKO® and declined −2.4% (−2.80, −2.05) in those not on the drug. Among those on SYMDEKO®, FEV_1% improvement varied by smoke exposure ($p < 0.001$). In unexposed subjects, FEV_1% increased 0.72% (0.03, 1.41), while in smoke-exposed it declined 1.03% (−2.5, 0.5). In fixed-effect models, FEV_1% improvement remained significant in unexposed subjects (0.5%; 0.08, 0.9, $p = 0.017$), while in smoke-exposed subjects there was no improvement (−0.44%; −0.20, 0.4, $p = 0.452$).
Conclusion: Smoke exposure blunts the therapeutic effect of tezacaftor/ivacaftor in CF patients ages 12–18 years. Future analysis will assess the consequence of smoke exposure in the recently FDA-approved triple-combination agent (elexacaftor/tezacaftor/ivacaftor, Trikafta®). Although findings need to be validated with biomarkers of smoke exposure and in other cohorts, these data suggest that limiting smoke exposure may help enhance the benefit of CFTR modulators.

WS13.4

Distribution of cystic fibrosis patients not eligible to studied CFTR modulators in Europe

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Studied Cystic Fibrosis (CF) modulators have been announced to cover 90% of all CF patients. A genotype-agnostic novel therapy for CF is under development, which will focus on people with CF who have mutations that are not eligible for the approved small molecule modulators and triple combination therapies. The data in the European Cystic Fibrosis Society Patient Registry (ECFSPR) are used to provide a quantitative overview of eligible patients.
Patients who are alive and seen during the 2017, or alive and not seen were considered (excluding France who delivered the data directly to the sponsor). Not considered were patients F508del homozygotes eligible for elexacaftor/tezacaftor/ivacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor, or heterozygotes eligible for elexacaftor/tezacaftor/ivacaftor. Neither were patients with at least one of the following mutations: E56 K, P67L, R74W, D110E, D110H, R117C, E193 K, L206W, R347H, R352Q, A455E, D579G, 711 +3A->G, E831X, S945L, S977F, F1052 V, K1060 T, A1067 T, R1070W, F1074L, D1152H, D1270N, 2789+5G->A, 3272-26A->G, 3849+10kbC->T (eligible for tezacaftor/ivacaftor, ivacaftor) and R117H, G178R, S549N, S549R, G551D, G551S, G1069R, R1070Q, G1244E, S1251N, S1255P, G1349D (eligible for ivacaftor).
From the 41,264 patients registered in the ECFSPR for the 2017, 4,798 patients (12%) carry a genotype that is not eligible to the currently approved modulators or the triple combo. The percentage of non-eligible patients varies from 2,3% in Ireland to 71,9% in Armenia. 2,954 of these patients are 11 years or older, 1,561 have a FEV1% of predicted value between 40% and 90%.
In Europe approximately 88% of the patients will be eligible for the currently approved modulators or triple combo, in some countries this percentage is below 50%. With the ECFSPR data, a realistic and useful overview could be created to support the design of a study for patients that are not eligible to the currently available modulator and triple combination therapies.

WS13.5

Access to treatments for people with cystic fibrosis across Europe: a 6-country pilot survey

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Objectives: Improved outcomes and survival for people with CF is owed largely to the success of therapeutic innovation and treatments available to manage symptoms. However, there is anecdotal evidence that access to key treatments varies greatly across countries and settings.
We aim to conduct a novel Europe-wide survey to describe variation in perceived access to medications for people with CF. This pilot survey stage aims to assess the acceptability and feasibility of a pan-European survey, ensure questionnaire items identify variability between and within countries, and generate a valid questionnaire that provides patient- and clinician-led perspectives on access to treatments.
Methods: The online pilot survey will be administered via SurveyMonkey to respondents from 6 CF Europe member countries - Belgium, France, Israel, Slovakia, UK and Poland.
Survey responses will be subjected to descriptive analysis, with primary focus on assessing feedback on wording and structure of the questionnaire.