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Real-life experience with a generic formulation of lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for the Phe508del *CFTR* mutation

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Introduction: Cystic fibrosis (CF) is caused by mutations that result in a deficient or dysfunctional cystic fibrosis transmembrane conductance regulator (CFTR) protein activity. Among CFTR modulators, potentiator compounds increase channel opening, whereas corrector compounds increase CFTR quantity in the cell surface.
Objective: To report real-life effects of a generic formulation of lumacaftor-ivacaftor use in patients with CF homozygous for the Phe508del CFTR mutation.
Patients and methods: Clinical variables (BMI, pulmonary exacerbations, sweat test, and pulmonary function) were analyzed in 30 CF patients homozygous for the Phe508del CFTR mutation, treated with lumacaftor-ivacaftor for 12 months, at the Respiratory Center of Hospital de Niños Ricardo Gutiérrez. These clinical variables were compared with those before the use of modulators.
Results: A total of 30 patients with CF homozygous for the Phe508del CFTR mutation receiving lumacaftor-ivacaftor therapy were included in this study. The mean age at the start of treatment was 10.8 ± 4.4 years. Nineteen patients were male. Before treatment, mean sweat chloride concentration was 87.8 ± 16.9 mEq/L, and it decreased to 75.2 ± 16.8 mEq/L ($p = 0.05$) 12 months after treatment. Mean BMI z-score improved from – 0.46 ± 0.94 to – 0.14 ± 0.88 ($p = 0.003$). A spirometry was performed in 28 of 30 patients. Mean FEV_1 was 83.1 ± 20.3 before treatment and 85.5 ± 23.96 after treatment ($p = 0.38$), 73.3% of patients referred less sputum production and 40% reported less dyspnea. 60% patients experienced at least one severe pulmonary exacerbation before treatment. while only 30% after treatment ($p = 0.037$).
Conclusions: The use of a generic formulation of lumacaftor-ivacaftor combination in patients homozygous for the Phe508del CFTR mutation was associated with improvement in nutritional status and respiratory symptoms, and a significant reduction in pulmonary exacerbations.

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Effect of Orkambi therapy on the lung microbiota in people with cystic fibrosis (PwCF) over the first 12 months of therapy (ROCK Study)

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Objectives: CFTR modulator therapy with Orkambi® (lumacaftor/ivacaftor) reduces the rate of decline of FEV_1 in people with cystic fibrosis (PwCF) homozygous for the F508del mutation. However, the effect of Orkambi® on the composition and structure of the CF airway microbiota remains unclear. In this study, we determined the effect of therapy with Orkambi® on lung microbiota composition.
Methods: PwCF (n = 37) from the Real-world Orkambi cohort Cork study (ROCK) in whom we previously have shown significant clinical improvements over 12 months [2], provided a sputum sample at baseline (pre-treatment) and at three-monthly intervals to a year post-treatment with Orkambi® (n = 196 samples). 16S MiSeq sequencing and clinical bacterial culture were performed in addition to qPCR for *P. aeruginosa, S. aureus* and *H. influenzae*.
Results: There was no change in the levels of detection of bacteria during the study as determined by NGS, sputum culture and qPCR (Table 1). There was no significant difference in relative abundance of top 20 taxa ($p > 0.05$) or in community richness ($p = 0.39$) Shannon-Wiener diversity ($p = 0.86$), evenness ($p = 0.66$) or dominance ($p = 0.78$) between visits. Despite this there was a reduction in prescription oral ($p < 0.0001$) and IV antibiotics ($p < 0.0001$). For the main bacteria, good agreement was observed in detection between methods. However, significantly higher levels of *Haemophilus* spp. and *Streptococcus* spp. were detected by NGS compared to culture or qPCR, resulting from the lack of resolution to the level of species by NGS.
Conclusion: Orkambi® treatment did not change the lung microbiota, despite a reduction in antibiotic usage. This indicates that Orkambi® treatment is having an effect on frequency of infective exacerbations for PwCF.

References

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Lumacaftor/ivacaftor combination for cystic fibrosis patients in Bulgaria

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Objectives: Standard CF therapy is symptomatic and aimed primarily at maximal relief of symptoms and prevention of complications. Over the last decade, drugs aimed at correcting the defective protein - CFTR-modulators - have also appeared on the market. These drugs were still unauthorized for use in Bulgaria until 2022 and are prescribed according to established legal procedure. Since 2022 every homozygous for deletion F508 (dF508) could be treated with CFTRm – double combination IVA/LUM or triple combination ELT/TEZ/IVA in cases with extremely low lung function test results. We are presenting our experience with IVA/LUM combination in Bulgaria.
Methods: Currently we have 46 patients treated with IVA/LUM combination (who have been on IVA/LUM therapy for at least 6 months with the longest ones treated for 2 years and half).

Table 1 (abstract: P069).
Percentage (%) of positive results from NGS (to genera level), sputum culture and species-specific qPCR assays

	NGS*					Culture					qPCR				
	T0	T3	T6	T9	T12	T0	T3	T6	T9	T12	T0	T3	T6	T9	T12
P. aeruginosa	91.7	80.7	90.3	80.0	96.7	72.2	77.4	74.2	66.7	60.0	77.8	71.0	80.7	63.3	70.0
S. aureus	55.6	51.6	61.3	60.0	53.3	44.4	45.2	41.9	40.0	43.3	52.8	61.3	64.5	50.0	53.3
H. influenzae	38.9	41.9	54.8	43.3	53.3	2.8	3.2	3.2	6.7	3.3	11.1	3.2	9.7	6.7	20.0
S. marcesens	0.0	0.0	0.0	0.0	0.0	2.8	0.0	0.0	0.0	0.0	N/A	N/A	N/A	N/A	N/A
S. maltophilia	13.9	16.1	19.4	13.3	20.0	5.6	12.9	9.7	6.7	10.0	N/A	N/A	N/A	N/A	N/A
B. multivorans	2.8	3.2	3.2	0.0	3.3	2.8	3.2	3.2	3.3	3.3	N/A	N/A	N/A	N/A	N/A
P. mirabilis	0.0	3.2	6.5	3.3	6.7	0.0	0.0	3.2	3.3	3.3	N/A	N/A	N/A	N/A	N/A
Streptococcus spp.	100.0	96.8	100.0	90.0	100.0	0.0	3.2	3.2	3.3	0.0	N/A	N/A	N/A	N/A	N/A
A. fumigatus	N/A	N/A	N/A	N/A	N/A	8.3	19.4	16.1	6.7	16.7	N/A	N/A	N/A	N/A	N/A

*Classification to level of genera only.