What's hot that the other lot got

Freddy Frost

RESTORING CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR FUNCTION REDUCES AIRWAY BACTERIA AND INFLAMMATION IN PEOPLE WITH CYSTIC FIBROSIS AND CHRONIC LUNG INFECTIONS

Ivacaftor is a cystic fibrosis transmembrane receptor (CFTR)-directed treatment for people with cystic fibrosis (CF) and a G551D mutation (approximately 5% of the CF population). Treatment results in significant clinical benefits; however, the effects on the pulmonary microbiome are less well understood. Hisert *et al* (*Am J Respir Crit Care Med* 2017;195:1617–28) prospectively studied 12 subjects as they were initiated on ivacaftor. Sputum was collected at multiple times in the first week of treatment and then regularly for over 2 years. Airway inflammatory profile, *P. aeruginosa* sputum counts, quantitative PCR and changes in the 16S microbiome were all investigated. Rapid and significant reductions in the sputum inflammatory cytokines interleukin (IL)-8, IL-1B and neutrophil elastase were observed during the first week of treatment and continued to decrease over the subsequent 24-month follow-up. *P. aeruginosa* counts showed a 10-fold reduction (−1.67 $\log_{10}$ CFU/mL, 95% CI −2.39 to −0.96; P=0.006) in the first week of treatment. However, *P. aeruginosa* was not eradicated completely in any patient and in the second year of treatment counts began to increase again. A similar pattern was seen in the 16S analysis. The authors speculate *P. aeruginosa* may genetically diversify to adapt to the CFTR-restored environment; however, compliance to other medications such as antipseudomonals was not recorded. Despite marked clinical and physiological improvements associated with ivacaftor, chronic infection may remain a clinical concern necessitating ongoing therapy.

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TEZACAFTOR-IVACAFTOR IN PATIENTS WITH CF AND F508DEL

The efficacy of CFTR treatments targeted towards the common F508del mutation (approximately 90% of the CF population) have so far imparted a less favourable response than ivacaftor in those with a G551D mutation. Two studies published simultaneously in the *New England Journal of Medicine* reported findings from clinical trials of tezacaftor, a new F508del-directed CFTR modulator, in combination with ivacaftor in patients with the F508del mutation. In the randomised, double-blinded, placebo-controlled EVOLVE study (Taylor-Cousar *et al*, *N Engl J Med* 2017;377:2013–23), patients over the age of 12 and with two F508del mutations were randomised to receive placebo or tezacaftor-ivacaftor. Up to 509 subjects were randomised and 475 completed the 24 weeks' study. Tezacaftor-ivacaftor significantly improved lung function (+4.0% predicted FEV_1 (3.1–4.8), P<0.001) compared with placebo and reduced pulmonary exacerbation rate (35% absolute reduction in exacerbations per patient per year, P=0.005).

In the EXPAND study (Rowe *et al*. *N Engl J Med* 2017;377:2024–35), 248 subjects, this time with one F508del mutation and one residual function mutation, were randomised to a three-intervention crossover design where each patient received two of the three treatments (placebo, ivacaftor monotherapy and tezacaftor-ivacaftor) for 8-week periods. Primary endpoint was FEV_1 and principal secondary outcome was quality of life (measured with the revised CF questionnaire). Tezacaftor-ivacaftor combination improved lung function compared with placebo (+6.8% (5.7–7.8), P<0.001) and ivacaftor monotherapy (+2.1% (1.2–2.9), P<0.001). Exacerbation rates tended to be lower than placebo in the treatment groups without reaching significance.

In both trials, the adverse event rate was low and tezacaftor-ivacaftor was well tolerated. Together, these studies demonstrate clinical efficacy and safety of tezacaftor-ivacaftor in patients with CF with the most prevalent mutation. The promising short-term outcome results in the EXPAND study need validating in longer term studies with clear patient-centred outcomes and the high costs of these genotype-specific therapies need weighing against the moderate improvements seen in the EVOLVE study before widespread clinical use.

PROTECTED SAMPLING IS PREFERABLE IN BRONCHOSCOPIC STUDIES OF THE AIRWAY MICROBIOME

Modern sequencing techniques have allowed a greater appreciation of the bacterial and fungal community in the lungs; however, the influence of potential contamination on sampling is not fully understood. Grønseth *et al* (*ERJ Open Res* 2017;3. doi:0.1183/23120541.00019-2017) investigate the influence of protected bronchoscopic sampling techniques on microbiome diversity. Fifty-eight controls, 64 subjects with stable COPD and 3 with stable asthma gave an oral washout sample and then underwent bronchoscopy with sequential brushings and lavage using both protected and unprotected techniques. Protected techniques involved an extra sterile inner catheter with a waxed tip being passed inside the bronchoscope channel. Bacterial composition was identified by sequencing of the 16S rRNA gene. Protected samples had increased differentiation from oral washings when compared with unprotected samples (P<0.01). This study confirms that unprotected bronchoscopic sampling is likely to result in the inclusion of oral flora. Although of importance for research into the lung microbiome the clinical significance remains unclear.

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