Miglustat therapy ameliorates bone mass and bone formation in F508del cystic fibrosis mice

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In CF patients with the F508del mutation, vertebral fractures and subsequent dorsal kyphosis decrease pulmonary function, thus accelerating the course of the disease. We discovered a defective CFTR-mediated Cl− channel activity and deficit of osteoprotegerin production by primary osteoblasts (the cells that form bone) of a 25-yr-old CF male (Gimenez A., 2012). Homozygous F508del-CFTR mice exhibit a severe osteopenic phenotype (Le Henaff C., 2012). Miglustat (N butyldexony-jirycin) was reported to normalize CFTR-dependent chloride transport in nasal mucosa in F508del CF mice.

We evaluated the efficacy of oral miglustat treatment in restoring bone mass in CF mice. The bone microarchitecture of CF mice, relative to wild type (WT) littermates was evaluated after an administration of 120 mg/kg/day miglustat for 28 days using micro-CT, bone histomorphometry and dynamic parameters of bone formation. Levels of two serum growth factors, insulin-like growth factor 1 (IGF-1) and 17b-estradiol (E2) were determined.

A once-a-day oral treatment with miglustat normalized bone volume and improved bone micro-architecture of the lumbar spine in CF mice after 4 weeks. This increase of bone volume was accompanied to both an increased bone formation and serum E2 level with no changes in IGF-1 level in miglustat-treated F508del mice. This study provides first evidence that oral administration of miglustat increases bone mass and formation in CF mice; these findings support the therapeutic potential of miglustat in patients with CF-related bone disease.

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Clinical outcomes and patient satisfaction following initiation of the TOBI Podhaler in CF adults

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Background: In the clinical trial setting, TOBI Podhaler (TIP) has been shown to be non-inferior to nebulised Tobramycin Inhalation Solution (TIS) in CF subjects. There is little ‘real world’ evidence of tolerance and effectiveness of TIP.

Aim: To assess the experience of CF adults receiving TIP at our large regional UK adult CF centre.

Methods: We report the results of a prospective observational study to evaluate changes in lung function and quality of life of 130 CF adults who have completed a trial of TIP. Patients also completed a visual analogue score (VAS) of satisfaction, ease of administration and likelihood to continue (1 = positive, 10 = negative).

Results: Adverse events (AEs) were reported by 26% at trial, most commonly cough (n = 31, 24%). Only 3 patients discontinued at trial, due to a ≥10% drop in FEV1% predicted. To date 83 patients have completed 1 cycle of TIP, with median change in FEV1% predicted of −3% (p = 0.08). 64% (n = 53) reported AEs; most commonly cough (n = 18, 22%). 27% commenced on oral or IV antibiotics for pulmonary exacerbation. Median VAS for satisfaction, ease of administration and likelihood to continue were all 1/10. Quality of life in the treatment burden domain of the CFQ-R increased by a median of 11.2 (p = 0.1). 27/130 patients to date have discontinued TIP before completion (n = 23) or at completion (n = 4) of their 1st cycle. 14 (52%) of whom were previously intolerant of TIS. The most common reason for discontinuation was cough (n = 19, 27%).

Conclusion: Despite a high incidence of adverse events, patients commencing TIP report high levels of treatment satisfaction and a trend towards perceived reduction in treatment burden.

Comparison of pharmacy prescription refill frequency in CF adults before and after switching from tobramycin inhalation solution (TIS) to TOBI Podhaler – ‘Real world’ evidence of improved adherence

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Objective: To assess the experience of CF adults receiving TIP at our large regional UK adult CF centre. We retrospectively analysed prescription refill data for all CF adults that had been switched from TIS to TOBI Podhaler at our large UK centre from January - October 2012. Prescription refill frequency was defined as the median number of refills collected per month before and after switching medication. For all patients, our centre was the sole supplier of TIS and TOBI Podhaler. 23 patients (10 male) switched from TIS to TOBI Podhaler over the study period. All patients were chronically infected with P. aeruginosa and chose to switch to TOBI Podhaler due to expected lower treatment burden. All patients had been taking TIS for 12 months or more before switching and the median (IQR) duration on TOBI Podhaler was 3.0 (1.5–3.6) months. Prescription refill frequency significantly increased following switching to TOBI Podhaler (median (IQR), 0.68 (0.52–0.95) vs. 0.25 (0.04–0.42) prescriptions/month (p = 0.04)).

Conclusion: Prescription refill frequency significantly increased in the first few months after switching from TIS to TOBI Podhaler, which is likely to reflect improved adherence. It is yet to be determined whether this initial finding is maintained in the longer term and whether this leads to improved clinical outcomes.