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| **Modulators and Cystic Fibrosis-Related Diabetes – What’s the Difference?** |
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| **Introduction/Aim:** Cystic Fibrosis-Related Diabetes (CFRD) affects up to 20% of children aged >12 years and 50% of adults with cystic fibrosis. It contributes to significant morbidity and a sixfold increased mortality in CF. Emerging evidence has highlighted the role of the CFTR protein in CFRD pathogenesis through its regulation of insulin secretion and chronic inflammation. CF modulator therapy, which targets the defective CFTR protein, could therefore mitigate or even reverse the CFRD disease process. There is significant potential to attenuate early pancreatic disease in the paediatric population, many of whom have access to modulator therapy early in life prior to the onset of CFRD.  Despite major improvements in pulmonary and nutritional outcomes with the advent of CF modulator therapy, there is a paucity of data outlining its impact on CFRD, particularly in the paediatric population.  We aimed to describe our cohort of paediatric patients with CFRD, and compare demographic and clinical data between those treated with CF-modulator therapy and those not currently on modulator therapy.  **Methods:** We performed a retrospective analysis of the medical records and continuous glucose monitoring (CGM) data for all paediatric patients with a diagnosis of CFRD under the care of our centre in July 2023. Patients were split into two groups, the modulator group (those on CF-modulator therapy at time of data collection), and non-modulator group (those not-on CF modulator therapy at time of data collection). Two-tailed, two-sample unequal variance t-tests were performed to compare the two groups.  **Results:** We identified n=24 children under the care of our service with a diagnosis of CF-Related diabetes. Of these, n=12 (54%) were on modulator therapy (n=11 on Kaftrio® (Elexacaftor/Tezacaftor/Ivacaftor), and n=1 on a clinical trial modulator drug). There was no significant difference between the average age of the modulator group (14 years), and non-modulator group (12 years) (p=0.3). In the modulator group there were 8 males (62%) and 5 females (38%), while in the non-modulator group there were n=5 males (45%) and n=6 females (55%). Of those on modulators, 92% were white vs. only 55% of those not on modulators. 8% of those on modulators were Asian vs. 36% of those not on modulators. Whilst average age of CFRD diagnosis was lower in the non-modulator group (9.4 years vs. 12.0 years), the difference was not statistically significant (p=0.11). There was no significant difference in HbA1C at diagnosis (p=0.13), percent time in-range on continuous glucose monitor at diagnosis (p=0.9), insulin dose (measured in units/kg) (p=0.25), FEV1 at diagnosis (p=0.9), or FEV1 after 3 months of insulin therapy (p=0.31) between the modulator and non-modulator groups.  Of the 13 patients on modulator therapy, only n=1 was diagnosed with CFRD before starting modulator therapy. This child’s insulin requirements increased after starting Orkambi® (lumacaftor/ivacaftor). Overall the median time from start of modulator therapy to diagnosis of CFRD was 3 months.  **Conclusion:** Whilst modulator therapy has dramatically changed the landscape of CF, there is yet to be convincing evidence of a sustained impact on CFRD. Our study demonstrated no significant difference in diabetes control and lung function between those with CFRD on modulator therapy, and those not on modulator therapy. Interestingly, the majority of those on modulator therapy had been established on this treatment prior to developing CFRD. Our study highlights the need for further research into the impact of modulator therapy on CFRD, particularly in the paediatric population where there is potential for early, disease-modifying interventions.      **Grant Support: Nil** |