"Wolfram syndrome: from physiopathology to therapy." – Dr Benjamin Delprat, MMDN, Inserm U1198.

Overview

The meeting discussed Wolfram syndrome, focusing on its physiopathology and potential therapies. Benjamin Delprat presented his research from Inserm, Montpellier, highlighting the role of the WFS1 protein and its interaction with NCS1 and IP3R in cellular calcium transfer. He proposed gene therapy using self-complementary AAV9 vectors to overexpress NCS1 and pharmacological therapy targeting the sigma-1 receptor. Preclinical studies in zebrafish showed that NCS1 overexpression corrected mitochondrial impairment, while sigma-1 receptor agonists improved hyperlocomotion. Future work includes validating these findings in mouse models and identifying new sigma-1 receptor modulators.

“Preliminary results on the Tirzepatide monotherapy in Wolfram syndrome trial - Dr Guilio Frontino and Dr Amelia Caretto, IRCCS San Raffaele Hospital, Milan, Italy

Overview

Dr. Giulio Frontino and Amelia Caretto presented preliminary results from a trial on Tirzepatide monotherapy for Wolfram syndrome. The trial, involving 17 patients (including children and adults), showed stabilization of C-peptide levels in half of the patients, with a median increase of 15% over two years. Tirzepatide improved beta-cell function and reduced inflammation markers. However, retinal nerve fibre layer thickness

decreased in some patients, possibly due to pubertal hormonal changes. The trial also noted stable BMI and improved HbA1c levels. Side effects were mild and manageable, with no severe adverse events reported.

“Wolfram Syndrome Clinical Trials: Advancing Treatments from Medications to Gene-Editing” - Dr Fumihiko Urano MD, PhD. Samuel E. Schechter Professor in Medicine. Director, Wolfram Syndrome and Related Disorders Clinic and Study @ BJC HealthCare. Washington University School of Medicine

Overview

Dr. Fumi Urano from Washington University discussed Wolfram Syndrome clinical trials, focusing on advancing treatments from oral medications to gene editing. Wolfram Syndrome, a rare genetic disorder with a median age of onset at 6 for diabetes and 11 for optic nerve atrophy, affects 1 in 250,000 to 700,000 people. Dr. Urano highlighted the severity categorization system (1-6) based on mutation types and shared a case study of a patient with mild manifestations due to a common Ashkenazi Jewish variant. The study on AMX 35, a drug to mitigate endoplasmic reticulum stress, showed improved insulin production and glycaemic control in a 48-week clinical trial. Future steps include gene editing therapy and regenerative therapy.