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New insights in the TRAZELGA project for the adult type 1 Gaucher disease patients treated with eliglustat follow-up

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Eliglustat is a substrate reduction therapy approved for Gaucher disease type-1 adult patients. We designed a prospective follow-up post-authorization study (TRAZELGA [GEE-ELI-2017-01]) to evaluate uniformly this therapy's response, performing a follow-up every six months. Includes the evaluation in terms of safety and effectiveness, analyzing clinical parameters, image bone assessment, and plasmatic biomarkers: chitotriosidase activity was evaluated by fluorimetry, glucosylsphingosine [GluSph] concentrations by LC-MSMS and CCL18/PARC, C5a, C3, YKL-40, Cathepsin S, Hepcidin and Lipocalin concentrations by inmunoassay. A quality of life study (SF-36), disease severity score index evaluation (GD-DS3) and adverse effects are included. Patients all over Spain, treated by Eliglustat were included in the study. Non-parametric statistical analysis was performed and $p < 0.05$ was considered as statistically significant. At this moment, 38 patients are recruited: median age was 45.0 years, male-female ratio is 1:1, the most common genotype was NM_000157:[c.1226A > C] + [other damaging variant] (87%). CYP2D6 metabolizers' distribution was 3%, 9% and 88% for poor, intermediate and normal phenotypes, respectively. Spanish MRI score: 6.4 (0−21), T-score: −1.1 (−3,7-1,0). 13.2% patients were splenectomized, 21.1% present multimorbidities and/or poly-medications and, 15.8% complained fatigue as the main symptom before their inclusion. During treatment 34% patients reported grade 1 digestive discomfort and one of them suffered a Helicobacter Pylori infection. Two patients (5.3%) discontinued therapy due to adverse events. 30 patients completed the first year of treatment and a statistically significant decrease on GluSph ($p = 0.0001$) and an increase on Lipocalin-2 ($p = 0.01$) plasmatic levels were registered while the rest of plasmatic biomarkers maintains their values. A new evaluation of all biomarkers, bone mineral density, response to treatment, adherence and, adverse effects will be performed when all patients complete the first follow-up year and will be presented at the congress in case the paper is accepted. TRAZELGA (GZ-2017–11,713) received a grant from Sanofi Genzyme for its realization.

doi:10.1016/j.ymgme.2020.12.239

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Novel regulatory function of GCN5L1 in lysosomal tubulation and biogenesis

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Lysosomes are responsible for degradation of macromolecules through fusion with autophagosomes and endosomes. The consumed lysosomes are required to be regenerated through the process of autolysosomal reformation (ALR) and lysosome biogenesis. This project aimed to investigate the regulatory mechanism of GCN5L1 gene in lysosome tubulation (LT), a crucial step for ALR. GCN5L1 belongs to both BLOC1 and BORC multiprotein complexes and is involved in controlling lysosomal trafficking, however, the effect of GCN5L1 on lysosome tubulation remains largely unknown. Genetic ablation of GCN5L1 in the liver showed a dramatic increase in accumulation of autolysosomes, decrease in lysosome regeneration and absence of lysosomal tubulation. This phenotype suggests the possibility of disruption in lysosome tubulation which results in disturbance of the overall lysosome homeostasis. Interestingly, the genetic reintroduction of GCN5L1 rescues LT in GCN5L1 knockout hepatocytes. To investigate if GCN5L1 regulates lysosomal components, Lyso-IP method was used to purify lysosomes from WT and GCN5L1−/− hepatocytes followed by quantification of lysosomal protein expression profiles using label free LC-MS. Bioinformatic analysis revealed that expression of lysosomal protease, Cathepsin B, was reduced while there was a significant increase in autophagy-related proteins in GCN5L1 −/− hepatocytes. These results support that the autophagic flux may be blocked due to inefficient digestion of lysosomes which results in accumulation of autolysosomes in GCN5L1−/− hepatocytes. Consequently, the autolysosome-dependent mTORC1 activity was upregulated in GCN5L1−/− hepatocytes. Our findings suggest that GCN5L1 deficiency alters the lysosomal signaling and contents as well as their degradation. These findings support that GCN5L1 plays a novel regulatory role in lysosome biology and may be involved in pathological processes of lysosome related disease, such as storage diseases, hepatic and cardiovascular diseases as well as the immune system function.

doi:10.1016/j.ymgme.2020.12.240

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PR001 gene therapy increased GCase activity and improved neuronopathic Gaucher disease phenotypes

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