

TRAZELGA Project: Preliminary results of the prospective national-base multicenter study to standardize the follow-up of type 1 Gaucher disease patients treated with Eliglustat.

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Introduction

Type 1 Gaucher disease (GD1) is an autosomal recessive inherited disease caused by a deficiency of the lysosomal enzyme glucocerebrosidase (EC 3.2.1.45), which produces the accumulation of glucocerebroside mainly in macrophages and it causes the deterioration of the organs and tissues where it is stored [1]. A selective substrate inhibitor Eliglustat, was approved in European Union in 2015 as a treatment to adults with GD1. This therapy is based on substrate reduction, blocking the glucosylceramide synthase enzyme (EC 2.4.1.80) and generating a smaller amount of glucosylceramide [2], which facilitates the residual activity of the glucocerebrosidase (Fig 1).

In Spain we have design a prospective follow-up post-authorization study called TRAZELGA to ensure the traceability of eliglustat therapy in GD1 patients. Eliglustat's metabolism uses mainly CYP2D6 pathway, being dose-dependent on the metabolizing state of the patient. Poor, intermediate or normal CYP2D6 metabolizers (≈95% of patients) [3] can receive this therapy as a first-line therapy or switched from other treatments.

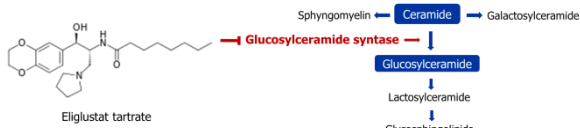


Figure 1: Action mechanism for Eliglustat. The molecule inhibits glucosylceramide synthase.

Aims

- To determine if the drug administration maintains or improves clinical goals and/or plasmatic biomarkers.
- To evaluate the treatment in terms of adverse effects, effectiveness and patient satisfaction.
- To run a protocol to standardize and analyze the outcomes of patients treated with eliglustat in clinical practice in Spain.

Patients and Methods

- Gaucher type 1 patients, treated with Eliglustat (according to the Summary of Product Characteristics (SmPC) [4]).

Biomarkers determination [5]

- Chitotriosidase activity (ChT)
- CCL18/PARC concentration
- Glucosylsphingosine concentration (GluSph)
- C5a complement factor concentration

Clinical and analytical

- Blood counts / Coagulation study
- Biochemical data
- Visceral volumes
- Bone assessment

Other determinations

- Quality of life study (SF-36)
- Disease severity score index evaluation (GD-DS3)
- Compilation of adverse effects

Statistics

- Software R version R-3.6.2
- Non-parametric test: sign test
- Statistically significant p<0.05

Results

Patients enrolled

- 38 patients were included.
- Age (median [P25-P75]): 52 (31.0-58.5) years old; n=29.
- 51% ♀ / 49% ♂.

Previous treatment

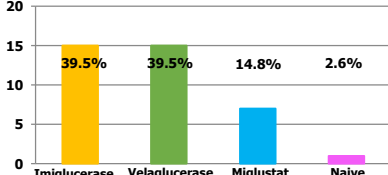


Figure 2: Previous treatment of 38 patients.

- Treatment time before switch (median [P25-P75]): 17 (8.5-23.0) years; n=37.
- CYP2D6 phenotype (Fig 3):

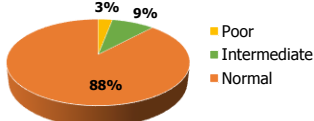


Figure 3: CYP2D6 phenotype of 38 patients.

Clinical and analytical data

Data from 38 patients at inclusion:

- 5 (13.2%) splenectomized patients.
- 6 (15.8%) with multimorbidities/poly medications.
- 6 (15.8%) complained fatigue as the main symptom.
- S-MRI score (median [P25-P75]): 6.4 (0.0-21.0).
- T-score (median [P25-P75]): -1.09 (-3.7-1.0).

Adverse effects: From the 38 enrolled.

- 13/38 (34.2%) grade 1 digestive discomfort.
- 1/38 (2.6%) *Helicobacter Pylori* infection.
- 2/38 (5.3%) cessation of Eliglustat by diarrhea.

• *GBA* genotype: According to the reference sequence NM_000157 (Fig 4).

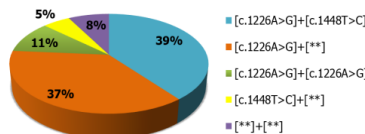


Figure 4: *GBA* genotypes of 38 enrolled patients. [**]: other pathogenic variant (nor c.1226A>G neither c.1448T>C).

Biomarker outcomes

Data from 25 patients with **completed follow-up**:
• Only GluSph shows a significant reduction (p=0.01) comparing one year treatment values with basal ones.

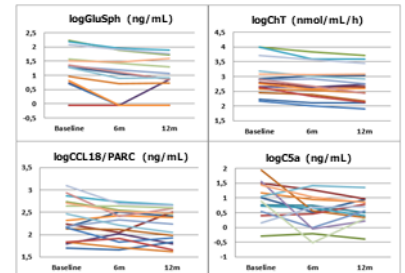


Figure 5: Biomarker values obtained every six months during 1 year.

	ChT nmol/mL/h	CCL18 ng/mL	GluSph ng/mL	C5a ng/mL
Baseline	3/23	14/25	9/24	12/21
12 months	2/23	13/25	11/24	12/21
Range (P10-P90)	17.0-113.0	28.0-158.4	<0.88	5.5-62.2

Table 1: Number of patients with normal intralaboratory values. 2 patients have no ChT activity and C5a of 4 patients remains to be analyzed.

Conclusions

Biochemical biomarkers maintains the values previously obtained, and GluSph reduce them significantly (p=0.01).

The reported adverse effects were generally mild or moderate.

All data will be assessed when all patients completed the time of the study.

References

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Funding: This work has been carried out with aid for research Sanofi-Genzyme GZ-2017-11713 and FEETEG.