Addendum II

Abstracts

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PLoS One. 2012;7(10):e47805

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Orphanet J Rare Dis. 2011 Oct 31;6:69

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Orphanet J Rare Dis. 2016 Mar 24;11:28

Lentiviral gene therapy using cellular promoters cures type 1 Gaucher disease in mice

Mol Ther. 2015 May;23(5):835-44

Long-Term Effect of Antibodies against Infused Alpha-Galactosidase A in Fabry Disease on Plasma and Urinary (lyso)Gb3 Reduction and Treatment Outcome

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Abstract

Introduction: Enzyme replacement therapy (ERT) with alpha-Galactosidase A (aGal A) may cause antibody (AB) formation against aGal A in males with Fabry disease (FD). Anti agalsidase ABs negatively influence globotriaosylceramide (Gb3) reduction. We investigated the impact of agalsidase AB on Gb3 and lysoGb3 and clinical outcome in Fabry patients on ERT.

Methods: Adult male and female patients on ERT for at least one year were included. Urinary Gb3 was measured by HPLC, plasma lysoGb3 by LC-ESI-MS/MS and AB with a neutralization assay.

Results: Of the 59 patients evaluable patients, 0/30 females and 17/29 males developed anti-agalsidase antibodies (AB+). Only 3/17 males had transient (low) titers (tolerized). All AB+ patients developed antibodies during the first year of treatment. Change of agalsidase preparation (or dose) did not induce antibody formation. AB+ males had significant less decline in plasma lysoGb3 compared to AB2 males ($p = 0.04$). Urinary Gb3 levels decreased markedly in AB2 but remained comparable to baseline in AB+ males ($p<0.01$). (Lyso)Gb3 reduction in plasma and urine on ERT was correlated with LVmass reduction in females and development white matter lesions and stroke.

Conclusion: In male patients antibodies against aGal A remained present up to 10 years of ERT. The presence of these antibodies is associated with a less robust decrease in plasma lysoGb3 and a profound negative effect on urinary Gb3 reduction, which may reflect worse treatment outcome.

Citation: Rombach SM, Aerts JMFG, Poorthuis BJHM, Groener JEM, Donker-Koopman W, et al. (2012) Long-Term Effect of Antibodies against Infused Alpha- Galactosidase A in Fabry Disease on Plasma and Urinary (lyso)Gb3 Reduction and Treatment Outcome. PLoS ONE 7(10): e47805. doi:10.1371/journal.pone.0047805

Editor: Rajesh Mohanraj, UAE University, Faculty of Medicine & Health Sciences, United Arab Emirates

Received April 24, 2012; **Accepted** September 17, 2012; **Published** October 19, 2012

Funding: This study was funded by The Netherlands Organization for Health Research and Development (ZON-MW). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: GEL, FAW, JMA and CEMH have received reimbursement of expenses and honoraria for lectures on the management of from Genzyme, Actelion and Shire HGT. GEL, JMA and CEMH donated the honoraria to the Gaucher Stichting, a foundation that supports research in the field of lysosomal storage disorders. All other authors declare no conflicts of interest. This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials.

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Consequences of a global enzyme shortage of agalsidase beta in adult Dutch Fabry patients

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Abstract

Background: Enzyme replacement therapy is currently the only approved therapy for Fabry disease. From June 2009 on, viral contamination of Genzyme's production facility resulted in a worldwide shortage of agalsidase beta leading to involuntary dose reductions (approved dose 1 mg/kg/eow, reduced dose 0.5 mg/kg/m), or switch to agalsidase alpha (administered dose 0.2 mg/kg/eow). An assessment report from the European Medicines Agency (EMA) raised serious concerns about an increase in adverse events at lower dosages of agalsidase beta. We determined the influence of the shortage on clinical event incidence and the most sensitive biochemical marker (lysoGb3) in Dutch Fabry patients.

Methods: The incidence of clinical events per person per year was calculated from start of agalsidase beta treatment until the shortage, and was compared to the incidence of clinical events during the shortage period. In addition, plasma lysoGb3, eGFR, quality of life (SF-36) and brief pain inventory (BPI) questionnaires were analysed.

Results: All thirty-five Dutch Fabry patients using agalsidase beta (17 males) were included. Mean clinical event incidence was unchanged: 0.15 events per person per year before versus 0.15 during the shortage ($p = 0.68$). In total 28 clinical events occurred in 14 patients during 4.6 treatment years, compared to 7 events in 6 patients during the 1.3 year shortage period. eGFR and BPI scores were not significantly altered. Two SF-36 subscales were significantly but minimally reduced in females. In males, lysoGb3 increased with a median of 8.1 nM (range 2.5 - 29.2) after 1 year of shortage ($p = 0.001$). Increases in lysoGb3 were found in both patients switching to agalsidase alpha and on a reduced agalsidase beta dose. Antibody status, treatment duration or clinical event incidence showed no clear correlation to lysoGb3 increases.

Conclusions: No increase in clinical event incidence was found in the adult Dutch Fabry cohort during the agalsidase beta shortage. Increases in lysoGb3, however, suggest recurrence of disease activity.

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Biochemical response to substrate reduction therapy versus enzyme replacement therapy in Gaucher disease type 1 patients

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Abstract

Background: We retrospectively compared biochemical responses in type 1 Gaucher disease patients to treatment with glycosphingolipid synthesis inhibitors *miglustat* and *eliglusta*t and ERT.

Methods: Seventeen GD1 patients were included (n = 6 eliglustat, (two switched from ERT), n = 9 miglustat (seven switchers), n = 4 ERT (median dose 60U/kg/m). Plasma protein markers reflecting disease burden (chitotriosidase, CCL18) and lipids reflecting substrate accumulation (glucosylsphingosine, glucosylceramide) were determined. Also, liver and spleen volumes, hemoglobin, platelets, and fat fraction were measured.

Results: In patients naïve to treatment, chitotriosidase, CCL18 and glucosylsphingosine decreased comparably upon eliglustat and ERT treatment, while the response to miglustat was less. After 2 years, median decrease of chitotriosidase was 89 % (range 77–98), 88 % (78–92) and 37 % (29–46) for eliglustat, ERT and miglustat naïve patients respectively; decrease of CCL18 was 73 % (63–78), 54 % (43–86), and 10 % (3–18); decrease of glucosylsphingosine was 86 % (78–93), 78 % (65–91), 48 % (46–50). Plasma glucosylceramide in eliglustat treated patients (n = 4) reached values below the normal range (n = 20 healthy controls). Biochemical markers decreased or stabilized in switchers from ERT to eliglustat (n = 2), but less in miglustat switchers (n = 7). Clinical parameters responded comparably upon eliglustat and ERT treatment.

Conclusions: Our explorative study provides evidence that biochemical markers respond comparably in patients receiving eliglustat treatment and ERT, while the corresponding response to miglustat treatment is less.

Keywords: Gaucher disease, Eliglustat, Miglustat, Chitotriosidase, Glucosylsphingosine, Glucosylceramide, Enzyme replacement therapy

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Lentiviral Gene Therapy Using Cellular Promoters Cures Type 1 Gaucher Disease in Mice

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Gaucher disease is caused by an inherited deficiency of the enzyme glucosylceramidase. Due to the lack of a fully functional enzyme, there is progressive build-up of the lipid component glucosylceramide. Insufficient glucosylceramidase activity results in hepatosplenomegaly, cytopenias, and bone disease in patients. Gene therapy represents a future therapeutic option for patients unresponsive to enzyme replacement therapy and lacking a suitable bone marrow donor. By proof-of-principle experiments, we have previously demonstrated a reversal of symptoms in a murine disease model of type 1 Gaucher disease, using gammaretroviral vectors harboring strong viral promoters to drive glucosidase β-acid (GBA) gene expression. To investigate whether safer vectors can correct the enzyme deficiency, we utilized self-inactivating lentiviral vectors (SIN LVs) with the GBA gene under the control of human phosphoglycerate kinase (PGK) and CD68 promoter, respectively. Here, we report prevention of, as well as reversal of, manifest disease symptoms after lentiviral gene transfer. Glucosylceramidase activity above levels required for clearance of glucosylceramide from tissues resulted in reversal of splenomegaly, reduced Gaucher cell infiltration and a restoration of hematological parameters. These findings support the use of SIN-LVs with cellular promoters in future clinical gene therapy protocols for type 1 Gaucher disease.

Received 25 June 2014; accepted 22 January 2015; advance online publication 10 March 2015. doi:10.1038/mt.2015.16

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