Effects of switching from a reduced imiglucerase to velaglucerase in type 1 Gaucher disease: clinical and biochemical outcomes

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Online Supplementary Design and Methods

Data collection

Results for hemoglobin concentration, platelet count and chitotriosidase activity were collected at four different time points:

1. one year before the imiglucerase shortage (median 14.6 months, range 9.2-25.7);
2. at the last visit before the onset of the shortage (range from 10.1 months prior to the shortage to 0.3 months after the shortage);
3. at the last visit before the switch to treatment with velaglucerase (range from 2.7 months prior to the switch to 0.6 months after the switch);
4. after approximately one year of treatment with velaglucerase (median 11.9 months, range from 6.9 to 16.0 months);

The interval between time points 1 and 2 was 12 months (median range 9.4-15.6 months).

Values obtained before the shortage were compared with those obtained when the period of dose reduction was at its maximum, as well as with the results after one year of treatment with velaglucerase. One year of follow up on velaglucerase was chosen as a cut-off point, because this interval was felt to be in proportion to the maximum time patients were dose reduced. In addition, imaging results were collected every six months (Dutch patients only):

- spleen and liver MRI and QCSI images.

Hemoglobin level and platelet count

A reduction in hemoglobin concentration to less than 13.0 g/dL (males) or 12.0 g/dL (females) ánd of more than 1.0 g/dL, was considered significant. A (clinically) significant decline in platelet levels was defined as a reduction to less than $150x10^9$/L and a decrease of more than $20x10^9$/L.

Chitotriosidase activity

Plasma chitotriosidase activity was measured using the 4MU-deoxychitobioside substrate as described by Aguilera *et al.*[1] and slightly modified by Schoonhoven *et al.*[2] for Dutch patients. For UK patients, the 4MU-chitotrioside substrate was used.[3] Chitotriosidase activity measured with the 4MU-chitotrioside assay results in lower values as compared to the 4MU-deoxychitobioside substrate because of an apparent substrate inhibition effect. A previous study established that there was a difference in deoxychitobioside/chitotrioside ratios between individual patients from 1.6 to 3.4, but are intra-individually very constant.[4] Relative changes in chitotriosidase activity were calculated to allow for a comparison of response patterns.

An increase/decrease in chitotriosidase activity of 30% compared to baseline (before the shortage) was considered significant. Thirty percent was used as a cut-off value based on the inter-assay variation for these assays. Using the 4MU-deoxychitobiose substrate in the Amsterdam laboratory the inter-assay coefficient of variation (cv) was 9.8%. Using the 4MU-chitotrioside substrate in the Cambridge laboratory the inter-assay cv was 4.0%.

Stability of the measurements of chitotriosidase activity in plasma samples was found to be excellent for a period of four years (cv <15%).

Imaging

All Dutch patients who switched to treatment with velaglucerase underwent MRI scans at baseline (defined as five months prior to switch up until maximally one month after switch) and every six months after switching to assess organ volumes.

Bone marrow involvement was assessed by measuring the bone marrow fat fraction using Dixon's Quantitative Chemical Shift Imaging (QCSI) of the lumbar spine.[5,6] De Fost *et al.*, in a prospective analysis of the effects of a low frequency maintenance regimen, used a relative change of 20% or more in QCSI as one of the criteria for disease progression based on an observed standard deviation of variability in a stable cohort of 4.1%.[7] A relative change of 20% or more was, therefore, considered significant.

Statistical analysis

For statistical calculations, the SPSS 16.0 software package was used. Mann-Whitney U tests were performed to compare characteristics of patients showing progression of disease and patients who were stable during the period in which their dose was reduced.

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