IMIGLUCERASE SHORTAGE: EFFECTS ON PATIENTS WITH GAUCHER's DISEASE

Poster No.: P-0146
Congress: ESSR 2013
Type: Scientific Exhibit
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Keywords: Musculoskeletal bone, MR, Treatment effects, Image verification
DOI: 10.1594/essr2013/P-0146

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Purpose

Gaucher cells are macrophages that are lipid-laden due to a deficiency of the enzyme glucocerebrosidase; the lipids tend to accumulate in those places where these cells are normally located, one of the most important locations being bone marrow. The appearance of normal bone marrow in Magnetic Resonance Imaging (MRI) is basically due to its lipid content, and is characterised by a marked hyper-signal in T1, an intermediate signal intensity in T2 and a complete loss of signal in the fat saturation ("Fat-Sat") or STIR sequences. Therefore, the infiltration of bone marrow by pathological Gaucher tissue appears as a loss of signal intensity in both T1 and T2, although more obviously in T1. Consequently, these sequences are often the most useful for diagnostic purposes, as they very accurately indicate the spread of the affected area, which in the early stages of the disease is usually advanced in the axial skeleton and more variable in the peripheral skeleton, in line with the usual centrifugal pattern of disease spread. The degree of bone marrow infiltration has therefore traditionally been monitored by means of MRI. Qualitative, quantitative and semi-quantitative systems of classification and comparison have been proposed which largely facilitate therapeutic control, determining the required maintenance dose (which usually varies from one patient to another depending on the degree of affection), and detecting intercurrent complications.

Enzymatic replacement therapy with recombinant human glucocerebrosidase (imiglucerase, Cerezyme® Sanofi/Genzyme) may prevent the development of irreversible bone complications and, above all, usually corrects the pathological infiltration of the marrow, with the signal hypo-intensity of the marrow in T1 progressively clearing until a situation of "balance" is reached, usually after a year of treatment. This balance is usually maintained in the subsequent MRI monitoring, which in our sphere is normally undertaken twice-yearly in the stable patient.

In June 2009, the company Sanofi/Genzyme was forced temporarily to close its plant in Allston (Boston) when a Vesivirus infection was discovered in one of its bioreactors, causing a prolonged shortage of the product for the more than 8,000 Gaucher disease patients throughout the world. During the following months, the product reserves had to be prioritized for the more serious patients, until normal production of the recombinant enzyme was resumed at the end of 2010.

Firstly, this paper retrospectively assesses the effects observed in the bone marrow of our patients caused by the interruption of the enzyme replacement therapy in the period between September 2009 to October 2010. During this time, the dwindling stocks of the product were reserved for use with the more serious patients, albeit, in the best of cases, at lower doses than those usually used for therapeutic maintenance. Secondly, the work also assesses the degree of response observed in those patients who had a second
MRI check once appropriate treatment doses were restored, based on their radiological evolution.
Methods and Materials

Fourteen patients with Gaucher's disease underwent long-term enzyme replacement therapy in our hospital. The 8 men and 6 women, aged between 24 and 56 years, were all diagnosed between 1995 and 2007. Only one corresponded to the type III variety ("sub-acute neuronopathic"), and this person was excluded from this paper, in order to standardize the sample. The remaining thirteen patients were type I Gaucher ("non-neuronopathic"), and had been receiving imiglucerase therapy for at least six years prior to the supply shortage. All of them had been clinically, biochemically and radiologically stable for at least four years before production of the enzyme was abruptly interrupted. Of these thirteen patients, five were excluded from the study for not having had a previous MRI scan, or for displaying results with artifacts. The remaining eight were all radiologically monitored using a Philips Intera 1.5 T MRI system, according to the service protocol (sagittal series of the complete column in T1, T2 and STIR, and coronal alignment of the complete lower limbs in T1, T2 and STIR, applying the "MovieTrack" system to scan extensive anatomical areas). The retrospective assessment of these studies was done on a DICOM workstation, from the consensus diagnosis obtained from two radiologists with more than 10 years of experience in the field of musculo-skeletal radiology. The comparison was made selectively on the T1 series of the spine, given this series' greater effectiveness in determining the degree of bone marrow infiltration, and the earlier involvement of the axial skeleton than the peripheral skeleton. In each patient, the last MRI scan prior to the beginning of the supply shortage (the "baseline MRI" scan) was compared with the first of the scans performed when the shortage ended (the "post-deprivation MRI" scan, performed in a period of between 12 and 20 months from September 2009). This established the qualitative progression categories of "null, mild or severe". To assess the reversibility of the pathological infiltration following the resumption of treatment, in three of the cases we were able to compare this second study with a third MRI scan, performed between 17 and 22 months after the previous scan (the "post-resumption" MRI). Results were classified "improvement" or "no-improvement". Finally, the paper assesses the results obtained, taking into account the degree of enzyme deprivation suffered by each patient based on the severity of their baseline organic involvement.
Results

In seven of the eight patients included in the study, a diffuse progression was confirmed in the infiltration of vertebral marrow by pathological Gaucher tissue when the post-deprivation images were compared with images corresponding to the baseline studies (Table 1). In principle, this is attributable to the deprivation of the enzyme, given the known radiological stability of all the patients beforehand. Four of those seven cases showed a slight pattern of progression (Figure 1), whereas the other three displayed an advanced degree of marrow re-infiltration (Figures 2 and 3). If the results are analyzed by dose reduction (partial or total, according to the severity of involvement in the baseline pathology), it is notable that severe marrow involvement was only found in one of the four patients who had been administered a small maintenance dose (25%), while the three remaining cases showing slight forms of progression (75%). Of the four patients who received no treatment during the 13 months of supply shortage, two cases had advanced marrow infiltration (50%), one showed signs of slight progression (25%), while the fourth, paradoxically, displayed null progression between the two scans (Figure 4). In the three cases in which a second MRI scan was performed (100%), a tendency to improve was confirmed following resumption of the usual enzyme dose (Figures 1 and 2), regardless of the size of the dose reduction (two partial and one total) and of the level of pathological progression (two severe and one mild).

When interpreting the results from a global point of view, although the small number of patients studied precludes statistical analysis, it nevertheless seems evident that, at least empirically, our observations point towards a very frequent reversibility of the therapeutic effects of the enzyme replacement therapy with imiglucerase on the bone marrow, once its periodic administration is interrupted (given that seven of the eight patients got worse). Our experience also suggests this pathological infiltration tends to revert once the enzyme is re-administered (as the three re-assessed patients improved). Despite the reasonable predictability of these conclusions, we found no similar references in existing bibliography, perhaps because Gaucher’s disease is a very low incidence disease (1/60,000 inhabitants) which is usually treated by enzyme replacement therapy characterised by high therapy adherence (given the quality of life which it normally confers on the patient). Indeed, the anomalous situation of a general product supply shortage was needed to be able globally to verify the organic effects of its interruption. Nevertheless, since the exception described above (possibly linked to the idiosyncrasy of each patient) calls into question the general validity of these conclusions, and it is necessary to design multicentric studies focussing on larger populations of patients with Gaucher’s disease. This would provide sufficient statistical significance for a convincing confirmation of our preliminary results, collating them by degree of enzyme dose reduction, correlating them with other biochemical and clinical disease monitoring indicators and enriching them with semi-quantitative or quantitative comparison tools capable of correcting the results taking into account the prior extent of the bone marrow involvement, and the degree of progression observed in pathological infiltration.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose Reduction</th>
<th>Progression of &quot;Baseline Deprivation&quot;</th>
<th>&quot;Deprivation Resumption&quot; Recovery **</th>
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</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Partial</td>
<td>Mild progression (20 months)</td>
<td>-</td>
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<tr>
<td>Patient 2</td>
<td>Partial</td>
<td>Mild progression (15 months)</td>
<td>-</td>
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<tr>
<td>Patient 3</td>
<td>Total</td>
<td>Null progression (12 months)</td>
<td>-</td>
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<tr>
<td>Patient 4</td>
<td>Partial</td>
<td>Severe progression Improvement (14 months) (22 months)</td>
<td>-</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Total</td>
<td>Mild progression (14 months)</td>
<td>-</td>
</tr>
<tr>
<td>Patient 6</td>
<td>Partial</td>
<td>Mild progression Improvement (16 months) (17 months)</td>
<td>-</td>
</tr>
<tr>
<td>Patient 7</td>
<td>Total</td>
<td>Severe progression (19 months)</td>
<td>-</td>
</tr>
<tr>
<td>Patient 8</td>
<td>Total</td>
<td>Severe progression Improvement (16 months) (21 months)</td>
<td>-</td>
</tr>
</tbody>
</table>

* Interval between the beginning of the deprivation and the date of MRI scan ("post-deprivation")

** Interval between "post-deprivation" MRI and "post-resumption" MRI scans
**Fig. 1:** (Patient 6). Sagittal series T1. Mild progression, with later improvement. Tenuous diffuse fall in the signal intensity of the vertebral bodies in B (Post-deprivation) with respect to A (Baseline), which becomes more evident with the disappearance of the small fat foci in bodies L3, L4 and L5. Tenuous diffuse signal recovery is confirmed in C (Post-resumption). This becomes more visible in comparison with the usually greater hypointensity of the inter-vertebral discs. Angiomatous formation persists in T9 in all cases.

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**Fig. 2:** (Patient 8). Sagittal series T1. Severe progression, with later improvement. Noticeable diffuse fall in the signal intensity of the vertebral bodies in B (Post-deprivation) with respect to A (Baseline). Partial diffuse recovery of the signal is also confirmed in C (Post-resumption), becoming more evident in the dorsal segment.

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Fig. 3: (Patient 4). Sagittal series T1. Severe progression. Noticeable diffuse fall in the signal intensity of the vertebral bodies in B (Post-deprivation) with respect to A (Baseline), traces of bone marrow fat persisting only around the Batson basivertebral veins. ). Partial diffuse recovery of the signal is also confirmed in C (Post-resumption).

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**Fig. 4:** (Patient 3). Sagittal series T1. Null progression. No significant changes observed in bone marrow signal intensity between the images of the baseline MRI (A) and those obtained after enzyme deprivation (B), despite its complete deprivation.

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Conclusion

The forced deprivation of enzyme treatment in the population of patients with Gaucher's disease, caused by the global enzyme supply shortage which followed the interruption of its production from September 2009 to October 2010, allowed us to confirm, in the majority of our patients, both the reversibility of the therapeutic effects of imiglucerase on bone marrow once its periodic administration is interrupted, and the tendency of this pathological infiltration to disappear following re-administration of this enzyme.
References


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