Interruption of enzyme replacement therapy in Gaucher disease

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In Australia, 58 patients with Gaucher disease were managed by a Gaucher Disease Advisory Committee (GDAC) through a centrally administered national programme, the Life Savings Drug Program (LSDP). In June 2009, Genzyme Corporation, which manufactures imiglucerase (Cerezyme), the only enzyme replacement therapy (ERT) registered for the treatment of Gaucher disease in Australia at that time, announced that due to a viral contamination problem there would be no further shipments of Cerezyme to Australia prior to the end of 2009. The GDAC allocated available drug supplies in order to maintain treatment to those most in need on a hierarchal clinical severity basis. A cohort of 24 patients with Type 1 Gaucher disease was withdrawn from therapy, 22 of whom had no discernible clinically significant adverse effects when reviewed off therapy for up to 6 months. In this paper, we review the course of 20 of the patients who have been on imiglucerase for periods of at least 24 months after the end of their 'drug holiday'. No patient experienced a bone crisis nor clinical nor magnetic resonance imaging evidence of new avascular necrosis events during this period. Two years after recommencing ERT after a 6-month drug holiday, no patient had developed an overt irreversible complication of their Gaucher disease, with the majority returning to their previous clinical status.

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Australian patients with lysosomal storage disorders who meet specific criteria receive enzyme replacement therapy (ERT) through the nationally administered Life Saving Drugs Program (LSDP) of the Commonwealth Department of Health and Ageing.[1] The Gaucher Disease Advisory Committee (GDAC) was a panel of medical experts appointed by the Department to advise on patient suitability for therapy, drug dosages and monitoring protocols. In June 2009, Genzyme Corporation, which manufactures imiglucerase (Cerezyme), the only ERT registered for the treatment of Gaucher disease in Australia at that time, announced that due to a viral contamination problem there would be no further shipments of imiglucerase to Australia prior to the end of 2009. On 11 August 2009, Genzyme further revised down its supply of Cerezyme to 20% of usual patient doses until the end of 2009. The GDAC allocated available drug supplies in order to maintain treatment to those patients most in need on a hierarchal clinical severity basis. A cohort of 24 type 1 Gaucher disease patients was withdrawn from therapy, 22 of whom had no discernible clinically significant adverse effects when reviewed off therapy for up to 6 months, as previously reported.[2] In January 2010, the 22 patients who had continued on the 'drug holiday' were able to recommence therapy, generally at reduced doses, when imiglucerase supplies improved. In this paper, we review the course of 20 of the patients who have been on imiglucerase for periods of at least 24 months after the end of their drug holiday. Two of 24 (8.5%) changed to another company's ERT during the drug holiday, 1/24 (4.25%) commenced substrate reduction therapy (SRT) due to problems with venous access and 1/24 (4.25%) moved overseas. It is reassuring that no patient has experienced an irreversible complication of their Gaucher disease, and over the 24-month period, most have shown return of their haematological and chitotriosidase levels to their stable 'pre-drug holiday' status and, in terms of skeletal parameters, most have stable magnetic resonance images (MRIs) that did not deteriorate over the period of the drug holiday.

Methods

Patients enrolled in the Australian government-funded ERT programme are required to sign a consent form permitting the collection of demographic, clinical and investigational data, their analysis by the GDAC and publication. All data analysis and publication are of de-identified information. All skeletal MRI scans are formally evaluated for bone marrow burden according to the scoring systems of Terk and Maas[3,4] by a single radiologist experienced in Gaucher disease imaging.[5]

Of the 24 type 1 Gaucher disease patients who were allocated to a drug holiday during the imiglucerase rationing period, two recommenced therapy with another company's ERT, on a clinical trial, prior to the end of the 6 months due to a deterioration of their clinical state. In January 2010, 6 months after the start of the drug holiday, the 22 patients who had remained on the drug holiday were able to access therapy, generally at reduced doses, when imiglucerase supplies improved. Twenty patients have received imiglucerase for at least 24 months after the end of their drug holiday. Two of 24 (8.5%) changed to another company's ERT, 1/24 (4.25%) commenced SRT due to problems with venous access and 1/24 (4.25%) moved overseas.

For statistical analyses, time 0 was immediately before starting the drug holiday. For percentage calculations, the values of all parameters analysed are allocated a score of 100% at time 0.

Results

Of the 20 patients, 11 (55%) were female, their mean age was 38 (range 18 - 77) years, they had been on imiglucerase ERT for a

mean of 9.2 (range 2 - 15) years. No patient developed a clinically detectable irreversible complication of their Gaucher disease up to 2 years after recommencing ERT after their drug holiday.

Considering the 20 patients who recommenced imiglucerase therapy after the drug holiday and were reviewed over the ensuing 24 months: their mean imiglucerase dose 24 months after recommencing ERT was 20.3 international units/kg/2 weeks (range 15 - 30 international units/kg) compared with a mean dose of imiglucerase of 21.8 international units/kg/2 weeks (range 15 - 33.6 international units/kg) prior to withdrawal of therapy.

Haemoglobin concentrations were normal in all 20 patients (100%) when ERT was withdrawn and remained in the normal range in all 20 (100%) at 24 months after recommencing therapy following the drug holiday. After restarting ERT, the mean haemoglobin percentage at 12 months was 99% (range 92 - 104%, *n*=20) and at 24 months 97.7% (range 88 - 109%, *n*=20) of pre-ERT cessation values, as shown in Fig. 1. Platelet concentrations were in the normal range in 18 patients (18/24, 75%) at the time of ERT cessation, remained in the normal range in 8/18 (44%) and became subnormal in 10/18 (56%) on the drug holiday. Considering the 20 patients followed up for 24 months: platelet concentrations were abnormally low in 12 patients (12/20, 60%) at the end of the drug holiday period and remained in the abnormal range in 2/12 (17%) and were in the normal range in 18/20 (90%). After restarting ERT, the mean platelet percentage at 12 months was 89.7% (range 73 - 127%, *n*=20), and at 24 months 99.7% (range 83 - 113%, *n*=18) of pre-ERT cessation values, as shown in Fig. 2. Two patients had symptoms of easy bruising and no patient experienced a clinically significant bleed.

Chitotriosidase was monitored in 17/20 (85%) patients, with 3/20 (15%) uninformative due to them being homozygous for the null mutations. Levels increased in all patients during their drug withdrawal; the mean chitotriosidase percentage increase at the end of the drug holiday was 443% (range 130 - 1 231%, *n*=17). After restarting ERT the mean chitotriosidase percentage at 12 months was 239% (range 77 - 508%, *n*=17) and at 24 months 97% (range 36 - 157%, *n*=16) of pre-ERT cessation values, as shown in Fig. 3.

We did not perform MRI studies specifically at either the time of cessation or restarting of therapy. The most recent MRI performed prior to cessation of therapy was, therefore, compared with the annual MRIs performed after restarting therapy. Twenty patients have had skeletal MRI follow-up ranging from 12 to 24 months after recommencement of therapy. At 12 months after recommencement of ERT, although 4/20 (20%) showed possible progression of their bone marrow involvement on the basis of increases in their semi-quantitative bone marrow burden (BMB) scores, at 24 months 16/17 (94%) showed stabilisation of their marrow involvement with no change from pre-drug holiday severity and 1/17 (6%) showed an improvement. None of the four patients showing possible progression of their bone marrow involvement on BMB scores at 12 months had bone-related symptoms or any features of new irreversible skeletal lesions, such as due to avascular necrosis, and 1/4

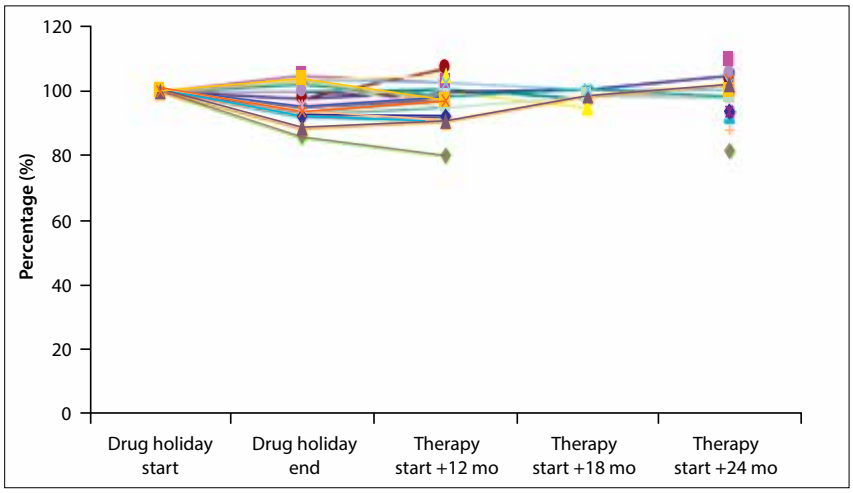

Fig. 1. Individual patient serial haemoglobin levels. Baseline represents level of 100% at time 0 when drug holiday commenced.

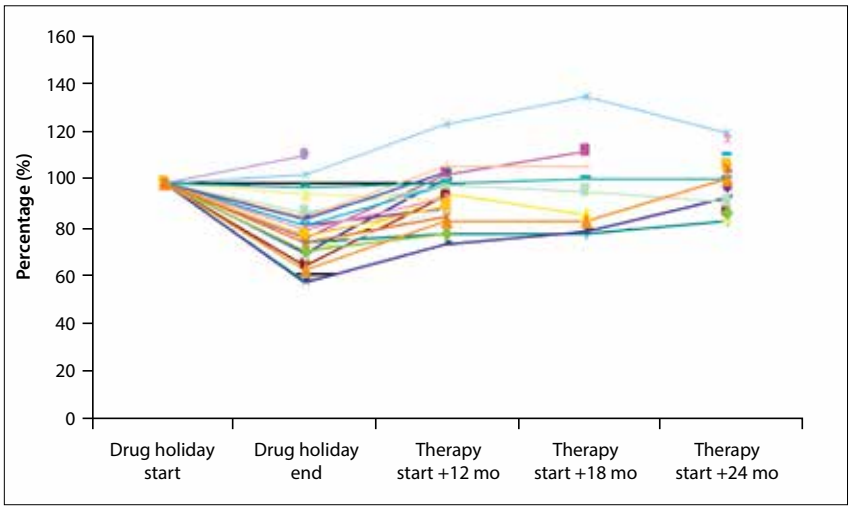

Fig. 2. Individual patient serial platelet counts. Baseline represents level of 100% at time 0 when drug holiday commenced.

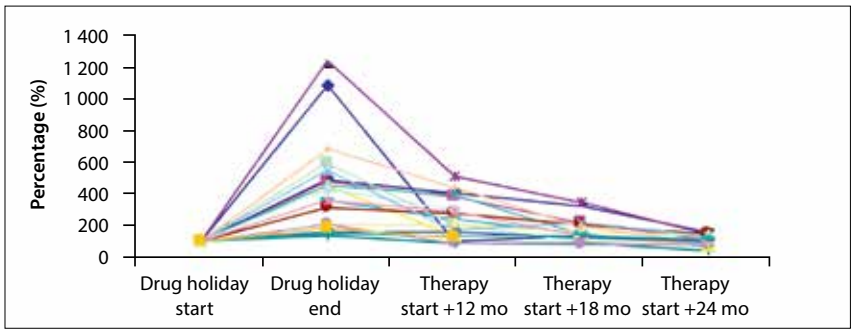

Fig. 3. Individual patient serial chitotriosidase levels. Baseline represents level of 100% at time 0 when drug holiday commenced.

showed improvement at the 24-month study, while the other 3/4 have not yet had MRIs subsequent to the 12-month review.

Eight patients complained that their symptom of fatigue had returned, three during the drug holiday and five subsequently. After restarting ERT, two patients experienced a recurrence of nonspecific limb pain, which had previously resolved on ERT, requiring reinstitution of non-steroidal anti-inflammatory therapy in one of them. These symptoms were also not associated with any clinical evidence of a new irreversible bone complication. No patient experienced any specific limb pain to suggest a Gaucher disease-related bone crisis. No patient showed an overt enlargement in liver or spleen size over the 24 months, as determined by clinical examination.

Discussion

These results suggest that it may be safe to withhold therapy in selected type 1 Gaucher disease patients who have initially been 'debulked' with ERT and show features of mild, stable disease. Continued and vigilant monitoring of such patients remains an essential part of the treatment regimen to prevent irreversible complications. Previous experience on the clinical stability of this cohort off ERT for up to 6 months suggested that studies of maintenance therapy without a no-treatment arm may lead to erroneous conclusions.[2] Furthermore, some selected patients may, owing to specific circumstances such as overseas travel, have treatment holidays or delayed infusions without short-term adverse outcomes.

This cohort of patients will continue to be closely monitored to ensure that none has developed subclinical complications during their drug holiday that might predispose them to future irreversible complications. If no long-term adverse effects are seen, such patients, and others rationed to lower doses, could be considered for more flexible and personalised dosage regimens in future. Although reassuring that skeletal clinical and imaging studies have remained stable following the drug holiday, long-term investigation of measures of skeletal involvement are necessary to confirm that there will be no detrimental effects in terms of bone disease.

ERT for Gaucher disease is generally considered life-long, with most treatment protocols recommending bi-weekly intravenous infusions, inconvenient for both patients and healthcare providers. There are also attendant infusion-related risks.[6,7] Further analysis of a larger cohort of patients previously on drug holidays should facilitate the development of international criteria for defining stable patients[8] who could be suitable for receiving maintenance therapy with longer intervals between infusions and consideration of sanctioned treatment-free periods, such as during periods of overseas travel, with appropriate monitoring.

The difficulty in assessing disease load, developing ERT criteria regarding who to treat and when to start, and assessing optimal, personalised, dosage regimens for both initial management and maintenance therapy, reinforces the role of multidisciplinary specialist physician expertise in investigating and managing patients with rare inherited metabolic disorders. The results of this study also emphasise the importance of individualised ERT dosing for patients with type 1 Gaucher disease manifesting variable phenotypic effects.

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