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Case Report

Treatment of profound thrombocytopenia in a patient with Gaucher disease type 1: Is there a role for substrate reduction therapy

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ABSTRACT

The availability of three enzyme replacement therapy (ERT) drugs and two substrate reduction therapy (SRT) drugs to treat Gaucher disease provides an opportunity to tailor therapies to a patient's specific clinical concerns. However, there is a gap in the literature regarding individual drug effectiveness in treating particular symptoms and the potential benefits of combination treatment.

This report details treatment of a patient with Gaucher disease type 1 whose main clinical concern was profound thrombocytopenia (around 20×10^9/L, normal range: 150–450 $\times 10^9$/L) with several episodes of bleeding with minimal trauma and bruises. The patient was treated with ERT at doses up to 60 units/kg weekly, with no improvement in platelet levels for 6 years. Subsequently, the patient transitioned to SRT and platelet levels increased almost two fold within the first month, and have remained stable at safe levels (30–60 $\times 10^9$/L) for almost 2.5 years at the time of publication.

This report demonstrates a possible therapeutic benefit of SRT in individual patients who do not meet therapeutic goals in terms of thrombocytopenia after a considerable period on first-line ERT treatment. Oral administration of SRT also improved this patient's quality of life allowing discontinuation of weekly ERT infusions, which better accommodated her demanding career and busy lifestyle.

1. Introduction

Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder caused by pathogenic variants in the gene *GBA* (OMIM #606463), resulting in deficiency of the enzyme glucocerebrosidase (glucosylceramidase 3.2.1.45) and pathogenic accumulation of the substrate glucocerebroside (glucosylceramide) [1,2]. Patients with GD manifest a spectrum of clinical abnormalities including pancytopenia, hepatosplenomegaly, and/or bone and bone marrow abnormalities. GD comprises three clinical types distinguished by the presence or absence of additional neurologic symptoms and the rate of progression; type 1 (non-neuronopathic), type 2 (acute neuronopathic), and type 3 (chronic neuronopathic).

Two primary treatment options currently exist for the somatic manifestations of GD, enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). ERT acts by intravenously providing recombinant glucocerebrosidase as either imiglucerase (Chinese hamster ovary cells), velaglucerase (human fibroblast cells), or taliglucerase (modified carrot cells). There are slight differences in amino acid sequence and posttranslational modifications among the three products, but the mechanism and overall effect of each is comparable [3–5]. In contrast, SRT treats GD by targeting the synthesis of glucocerebroside, and thereby reduces the amount of pathogenic substrate accumulation. Miglustat oral SRT was approved in 2003, but due to adverse events is only indicated for patients who cannot tolerate ERT [6]. Eliglustat, another oral SRT approved in 2015, has improved synthase specificity and thereby produces fewer adverse events [7,8]. Eliglustat has been approved as an alternative first-line treatment to ERT in adult patients with GD.

Prior research demonstrates that all three ERT and both SRT products are able to reach the overall therapeutic goals of improving cytopenia, reducing liver and spleen volumes, and managing bone symptom [5,9,10]. However, there is a gap in the literature regarding individual drug effectiveness in treating specific symptoms and the potential benefits of combination treatment [11]. With five drugs currently approved for treatment of GD type 1, there is potential to tailor therapies to an individual patient's clinical concerns.

Here we report our experience treating an adult patient with GD type 1 with persistently severe thrombocytopenia. The patient was treated with ERT and SRT, individually and concurrently, in an effort to realize maximum therapeutic benefit.

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2. Case report

The patient is a 47-year-old Ashkenazi Jewish female of Russian and Polish descent, born to non-consanguineous parents. She was diagnosed with Gaucher disease at age 39 via bone marrow biopsy. Genetic testing revealed homozygosity for the N409S (previously N370S) variant, confirming GD type 1. Her fraternal twin brother was subsequently also diagnosed with GD. The only other potentially relevant family history was a paternal grandmother with Parkinson's disease who died in her sixties.

At age 33, prior to the diagnosis of GD, the patient's gynecologist noted low platelets (below 20×10^9/L) during a routine visit, and referred her to hematology. Management of "idiopathic thrombocytopenia" with prednisone was unsuccessful. The hematology care team made the diagnosis of GD at age 39, and immediately initiated treatment with imiglucerase at 60 units/kg biweekly. The primary clinical concerns at the time of diagnosis were markedly enlarged spleen confirmed by a CT scan, profoundly low platelet levels with history of bleeds with minimal trauma, showers of spontaneous petechaie on a few occasions and easy bruising, and fatigue. The patient had no history of skeletal manifestations of GD, no neurologic symptoms of the disease other than occasional headaches or migraines, and normal cardiac structure and function.

After 14 months of regular treatment with imiglucerase at a dose 60 units/kg biweekly, there was an interruption in treatment due to national shortage of enzyme. The patient had a 3 month period of no treatment, followed by 3 months of regular treatment, and then 3 months of once monthly treatments. Concerns of persistent low platelets and ongoing fatigue led the patient to establish care at the Duke Metabolic clinic at age 40 years. A comprehensive workup at Duke noted bone scans negative for evidence of fractures, avascular necrosis, or other degenerative changes. Platelets counts were 16×10^9/L. The Gaucher biomarkers angiotensin converting enzyme (ACE) and tartrate resistant acid phosphatase (TRAP) were within normal ranges; chitotriosidase was elevated at 692 nmoles/h/mL (normal range: 4–120 nmoles/h/mL). MRI revealed a normal liver volume and enlarged spleen (1906 mL; 16 multiples of normal) with multiple lesions varying in size from 1 cm to 6.3 × 6.3.7.4 cm; there was no baseline volumetric MRI for comparison.

Treatment regimen was changed to imiglucerase 30 units/kg weekly (instead of the previous biweekly dose of 60 units/kg) to see if this would result in an increase in platelet counts. Platelet levels continued to show no improvement and hovered around 20×10^9/L for the next 3 months. In an attempt to improve the platelet response to ERT, dose of ERT was subsequently increased to 45 units/kg weekly and then to 60 units/kg weekly 3 months later. For the next 5 years, the patient was maintained on imiglucerase 60 units/kg weekly. At this weekly, higher dose, the patient reported increased energy levels, chitotriosidase decreased to 150–240 nmoles/h/mL (normal 4–120 nmoles/h/mL) and ACE and TRAP remained within normal ranges; however, platelet counts remained unchanged. Over the years on ERT, the patient noted several episodes of significant large bruises on her arms and legs. She also had intermittent episodes of rectal bleeds and hematuria. The patient also reported bleeding for several days following a dental cleaning. The patient is nulliparous and did not report menorrhagia, nose bleeds, or bleeding from gums. She did report occasional showers of spontaneous petechiae on the extremities. There continued to be no clinical concerns with bone health; liver volume remained within normal ranges. The spleen volume decreased to 1440 mL (from 1906 mL at age 40 years) at age 44 years at which time the platelet count was 21×10^9/L.

The referring hematologist and Duke metabolic clinic investigated comorbidities that might contribute to persistent thrombocytopenia despite a decrease in spleen volume. Coagulation abnormalities, antiplatelet antibodies, and Von Willebrand disease tested negative. Anti-Beta 2 Glycoprotein and anti-Cardiolipin, and lupus anticoagulant panel were all negative. As the patient never had infusion reactions and other disease parameters continued to improve on ERT, anti-imiglucerase or other drug neutralizing factors were not investigated.

Considering the patient's continued profound thrombocytopenia completely unresponsive after six years on ERT, especially given this patient's demanding profession and the occasional need to miss infusions due to work, maintaining the consistency of weekly ERT infusions was an additional concern and therefore consideration for adjunctive therapy with oral SRT using eliglustat was explored. SRT was a good option as the patient was a CYP2D6 intermediate metabolizer and had a normal heart rhythm on ECG. Treatment with oral eliglustat 84 mg twice a day (BID) was initiated along with ERT. The plan was to transition the patient slowly, given the significant thrombocytopenia and to see if there was an additive benefit. Within one month of combination therapy with imiglucerase 60 units/kg weekly and eliglustat 84 mg BID, platelet levels increased to above 30×10^9/L and chitotriosidase levels normalized. Concurrent treatment was discontinued after 2 months due to insurance limitations and financial burden. As the patient responded well to addition of SRT, and ERT alone for 6 years was ineffective in treating thrombocytopenia, ERT was subsequently discontinued and eliglustat 84 mg BID was continued as the sole treatment. One year after initiation of SRT, platelet counts were at 35×10^9/L and a repeat MRI showed an almost unchanged spleen volume of 1494 mL. At present, the patient has been on SRT for 2.5 years. The patient reports good compliance on oral treatment and denies any adverse effects. She reports less fatigability and fewer episodes of bruising with minor trauma, no rectal or dental bleedings or episodes of spontaneous petechiae, as was seen on ERT. Her platelets remain at levels up to 60×10^9/L ($30–60 \times 10^9$/L) thereby reducing the risk of spontaneous bleeding. While still enlarged, spleen volume at most recent follow-up has decreased in size approximately 64% from 1494 mL to 954 mL.

Since being on eliglustat, the patient has been in good overall health with less fatigue and improved endurance. Chitotriosidase has been within normal range, along with ACE and TRAP. All other hematological parameters including iron, vitamin B12, and folate are within normal ranges. She continues to be stable from a bone perspective, with no bone pain, crises, and normal bone density.

3. Discussion

Thrombocytopenia is one of the many multisystem manifestations of Gaucher disease. At baseline, approximately one in four patients have a platelet count below 60×10^9/L [12,13]. Levels below 20×10^9/L are considered severe [13]. The therapeutic goal for patients with platelet counts below 60×10^9/L at baseline is to increase counts by 2.5 fold in the first year with continuous increase thereafter and to a level sufficient to prevent surgical and obstetrical bleeding [10]. Platelet counts $> 30 \times 10^9$/L are rarely associated with spontaneous bleeds in Gaucher disease [9]. Some patients have been reported to have persistent thrombocytopenia despite ERT treatment for several years. Such cases of thrombocytopenia are usually associated with splenomegaly, and a reduction in spleen volume often results in improved platelet counts [14]. Evidence also suggests that patients with focal splenic lesions have worse thrombocytopenia and show less response to ERT [15].

The patient reported here presented with splenomegaly with multiple lesions and profoundly low platelet levels. Treatment goals were to increase platelet counts at the least to a level not associated with spontaneous bleeding ($> 30 \times 10^9$/L) and decrease spleen volume. Treatment with ERT at increasing doses over the course of several years successfully reduced spleen volume to below 1500 mL, but was ineffective in improving the patient's thrombocytopenia, which persisted at levels below 20×10^9/L.

Few recommendations exist for treating thrombocytopenia in GD. Splenectomy was the standard management prior to ERT [16]. There is now growing evidence that splenectomy increases the risk of other GD

manifestations such as bone disease, pulmonary hypertension, and malignancies [17–19]. This patient was advised against splenectomy, or even a partial splenectomy, due to these associated risks. Changing ERT products was discussed with the patient. However, the patient did not have infusion related reactions nor was there evidence that other products are more effective in treating thrombocytopenia. Once SRT eliglustat became commercially available, this option was explored to investigate a potential therapeutic benefit in treating thrombocytopenia. SRT was also preferred by the patient as avoiding weekly infusions would better accommodate her demanding career and busy lifestyle. Since transitioning from ERT to SRT, with a 2-month overlap, the patient's platelet counts have improved out of the severe range and the patient reports increased energy levels and less bruising. Platelet levels of patients who were naïve to GD treatment were shown to improve by 41% following initiation of SRT eliglustat [20]. Our patient, although not naïve to treatment but platelet counts being unresponsive, mirrored a similar response in which her platelet counts improved significantly and remained at closer to 60×10^9/L on SRT monotherapy for 2.5 years. A spleen volume after one year on SRT remained stable. A study by Hollak et al. determined a critical threshold of 1000–1500 mL in spleen volume for a platelet count $> 100 \times 10^9$/L [14]. Our patient reached the splenic threshold volume (1440 mL) but her platelets counts persisted to be $\leq 20 \times 10^9$/L, and thus was far away from the estimated platelet response. Beginning with dual therapy of ERT and eliglustat, our patient was successfully switched to eliglustat monotherapy with a good clinical and a relatively stable platelet response over 2.5 years. While this report may not allow for conclusions regarding optimal treatment of thrombocytopenia in GD, it highlights the possibility of differing responses to ERT or SRT treatment in individual patients. In order to delineate factors that contribute to treatment response and guide clinicians towards a personalized medicine approach, further investigation into treatment crossovers is needed.

4. Conclusions

A patient with GD type 1 whose main clinical concern was persistently low platelet levels with spontaneous and minor trauma induced bleeds since diagnosis, showed no improvement on high dose imiglucerase ERT for 6 years. Upon changing treatment to eliglustat SRT, platelet levels increased and are stable up to 60×10^9/L. This report demonstrates a possible therapeutic benefit of SRT in individual patients who do not meet therapeutic goals after a considerable period on first-line ERT treatment. In our patient there was an improvement in platelet counts along with improved quality of life due to the added benefit of an oral treatment, which better met the needs of this patient given her demanding career and busy lifestyle.

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