Anti-Taliglucerase Alpha Antibodies Associated with Lower Efficacy of ERT and Onset of Autoimmune Thyroiditis in a Patient with Type 1 Gaucher Disease

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Abstract

Treatment of patients with Gaucher disease type 1 with enzyme replacement therapy might be associated with development of anti-drug antibodies. As we know, the literature is lacking reports demonstrating the development of ADAs in patients with GD1 and association with a decreased efficacy, as was shown in other LSDs. We elaborate that high levels of ADAs in a patient with GD1 have impeded the hematologic endpoints and biomarker levels improvements and may have triggered autoimmune thyroiditis.

Keywords: Gaucher disease type 1; Enzyme replacement therapy; Anti-drug antibody; Taliglucerase alfa; Autoimmune disease.

Introduction

Gaucher Disease (GD) is one of the most frequent lysosome storage disease that affects glycolipids metabolism. It results from the deficiency of lysosomal acid beta glucocerebrosidase enzyme, due to mutations in GBA1. Gaucher disease is the first glycolipid storage disorder to be treated safely and effectively with intravenous glucocerebrosidase Enzyme Replacement Therapy (ERT) [1]. The decision to offer ERT in patients with non-neuronopathic Gaucher disease type 1 is based upon disease severity, as determined by the initial assessment, or significant disease progression, as demonstrated through regular follow-up [2]. Taliglucerase alfa is an ERT approved for the treatment of adult and pediatric patients with Type 1 GD (GD1). It is
the first plant cell-expressed recombinant therapeutic protein approved by the US Food and Drug Administration for humans. Studies report good efficacy and safety of taliglucerase alfa in treating patients with GD1, either children or adults [3-5]. Nevertheless, treatment with taliglucerase alfa can be associated with the production of anti-drug antibodies, generally not affecting the efficacy of the drug [5,6]. The purpose of this report was to show a case where the presence of high levels of ADAs in a patient with GD1 treated with taliglucerase alpha is associated with decreased efficacy and development of an autoimmune Hashimoto thyroiditis in this patient, which we believe had served as a trigger.

A 37-year-old female diagnosed with GD1 at the age of 29 years. The first signs of the disease appeared around 19 years old, with hemorrhagic skin manifestations, epistaxis and hepatosplenomegaly. Complete blood count showed thrombocytopenia and anemia, while bone marrow aspiration was interpreted as normal.

At the age of 23 years, the patient had a twin pregnancy that ended in spontaneous abortion followed by an extraterine pregnancy some months later. At 26 years old, she had a normal pregnancy, a successful C-section delivery that was complicated with high fever, thrombocytopenia and anemia. In consultation with gastro-hepatologist (due to suspicion for autoimmune hepatitis), the patient was treated with corticosteroids with minimal improvement.

**Diagnosis:** At 29 years old, due to persisting hematologic disturbances and the new onset of bone pain, another bone marrow aspiration was performed, which demonstrated the presence of Gaucher cells. The activity of the glucocerebrosidase enzyme was very low, which confirmed the diagnosis of Gaucher disease. Genetic testing identified the presence of c.1226A>G mutation (N370S, old nomenclature), as well as the double mutation of c.1342G>C (D409H, old nomenclature); c.882T>G (N370S, old nomenclature), thus the genotype N370S/D409H; H255Q (old nomenclature) was determined.

**Clinical evolution:** Treatment with ERT was associated with the gradual improvement of the hematologic parameters as well as with the improvement of the biomarkers (chitotriosidase and lyso-Gb1) performed at The Institute of Child Health, Athens, Greece and Centogene laboratory, Rostock, Germany, respectively (Figure 1). After more than two years of ERT with taliglucerase alfa, in May 2017, the patient reported a shortening of the menstrual cycle. At this time, the laboratory tests showed an increase of TSH to 10.2 µIU/ml (N= 0.4-4.0 µIU/ml) with the presence of anti-thyroid peroxidase antibodies (anti-TPO), 1690 UI/ml (N<34 UI/ml). An ultrasound of the thyroid gland demonstrated heterogenicity of the gland with micro and macro nodules, the largest of 8-10 mm. Thyroid’ scintigraphy revealed the presence of zones with different fixation of the radioactive contrast, with uptake at the minimum of normal levels. Based on these data, the diagnosis of autoimmune thyroiditis was established and levothyroxine was added to the treatment regimen. Further family history revealed several family members with autoimmune and/or inflammatory diseases, including rheumatoid arthritis, diabetes mellitus, thyroiditis, asthma and pancreatitis (Figure 2).

Laboratory testing performed at that time showed decreased platelet counts and decreased hemoglobin levels parallel to increased biomarkers levels (Figure 1). There were not noticed any change in liver and spleen volume as well as in parameters. In August 2018, ERT was switched to velaglucerase alpha. Laboratory tests show improved hematological parameters and decreased biomarkers level (Figure 1).

During treatment with taliglucerase alfa, blood samples have been drawn and preserved in 70 degrees every six months in order to be tested for the presence of anti taliglucerase antibodies, as part of our clinical protocol. Testing was enabled in January 2019 (Covance Laboratory, Indianapolis, USA), showing negative results during the first year of therapy with a progressive increase anti-taliglucerase alfa titers (Figure 1).

**Figure 1:** Changes over time of (a) platelet count, (b) hemoglobin level, (c) chitotriosidase, (d) lyso-Gb1 levels, (e) Anti-Taliglucerase antibodies levels.
The initiation of velaglucerase alfa was associated with improvement in ERT as reported by Elstein and Zimran [18,19]. In our patient, probable cross-reacted antibodies do not affect the efficacy of the therapeutic enzymes [17].

Treatment with ERT made her immune system more vulnerable to the therapeutic enzymes and intracellular misrouting of ERT [14,15].

In the present case, we show that high levels of ADAs can decrease the drug efficacy also in a patient with GD. As autoimmune thyroiditis developed at the same time, we suspected that the ADAs served as a trigger for the development of autoimmune thyroiditis. In Pompe disease and a lower rate of mucopolysaccharidosis I and are younger than 5 years: results of a multinational trial treated patients with Gaucher disease. Blood. 2011; 118: 22.

References


