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GAUCHER'S DISEASE

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ABSTRACT

Approved treatments for the lysosomal storage syndrome Gaucher's disease include enzyme replacement therapy (imiglucerase, Cerezyme®; Genzyme Therapeutics) and substrate inhibition therapy (miglustat, Zavesca®; Actelion Pharmaceuticals). These agents work by replacing the defective enzyme associated with Gaucher's disease (β-glucocerebrosidase [GCase]) and by targeting glucocerebroside, the fatty substance that accumulates as a result of defective GCase in the spleen, liver, kidneys, lungs, brain and bone marrow to cause severe clinical symptoms, respectively. This review focuses on new advances in the field of Gaucher's disease therapeutics.

INTRODUCTION

Gaucher's disease is the most common of the lysosomal storage syndromes, which are rare inherited metabolic disorders that result from defects in lysosomal function. Specifically, Gaucher's disease is characterized by genetic mutations that result in the production of a defective key enzyme, β-glucocerebrosidase (GCase). This leads to accumulation of its fatty substance glucocerebroside in the spleen, liver, kidneys, lungs, brain and bone marrow, which manifests as severe clinical symptoms. The disorder is named after the French physician Philippe Gaucher, who, in 1882, described a patient with a combination of leukopenia, thrombocytopenia and splenomegaly associated with hematopoietic malignancy. The underlying lysosomal abnormalities were not identified and characterized until 1965 (1). According to the National Gaucher Foundation (based in the U.S.), the carrier rate for the mutations that cause Gaucher's disease may be as high as 1 in 15 Jewish people of Eastern European ancestry, and 1 in 100 of the general population (2). This review summarizes the genetic and clinical features of Gaucher's disease, focusing on a review of current therapeutic developments.

GENOMICS AND PATHOGENESIS

Gaucher's disease is an autosomal recessive syndrome caused by genetic mutations that result in the production of misfolded GCase. This enzyme is responsible for the breakdown of glucocerebroside, a specialized fat molecule, to ceramide and glucose in the lysosome (3, 4). The genomics of Gaucher's disease have been established and three clinical subtypes have been described: type 1, which is non-neuronopathic and the most common form. It is prevalent in individuals of Ashkenazi Jewish descent (N370S missense mutation, with L444P representing the most frequent mutation in the Western hemisphere) (5); type 2 is the acute infantile neuropathic form that typically occurs within 6 months of birth; and type 3 is the chronic neuropathic form which can occur during childhood or adulthood. Type 3 Gaucher's disease has been isolated to the Norrbottnian population of Sweden (6) and other ethnic groups.

It was originally postulated that the high variation seen in the symptoms and characteristics of Gaucher's disease patient populations may be due to unique genotypes. However, despite the identification of approximately 300 individually associated mutations in the *GBA* gene, there does not appear to be a correlation between specific genotypes and phenotypes – this has been the subject of a full review by Hruska et al. (7). A recent study that analyzed unrelated patients from the Spanish Gaucher's disease registry (N = 193) also identified wide phenotypic variation among the 66 genotypes causing the disease in Spain (8).

Absent or defective GCase enzyme activity leads to the build-up of glucocerebroside inside certain cells, which can, over time, cause inflammation or damage to specific areas within the body, including the liver, spleen, bone marrow, lung and central nervous system (CNS) (5). Furthermore, a higher incidence of hematological and hepatic malignancies has been observed in type 1 Gaucher's disease patients (9). The clinical manifestations and diagnosis of Gaucher's disease have been reviewed in more detail in previous publications (10) and clinical studies are ongoing to further characterize the disorder (11-14).

TREATMENTS AND NEW ADVANCES

Enzyme replacement therapies (ERT)

Gaucher's disease is currently treated by the replacement of GCase (known as enzyme replacement therapy, or ERT). ERT with the placenta-derived alglucerase and the recombinant imiglucerase (Ceredase® and Cerezyme®, respectively, both from Genzyme Therapeutics) is administered as the standard of care in type 1 Gaucher's disease via intravenous infusion. More recently, there has been a shift from the use of Ceredase® to Cerezyme® due to the possibility of transmission of infective agents via placental tissue.

Cerezyme® is indicated for long-term ERT for pediatric and adult patients with a confirmed diagnosis of type 1 Gaucher's disease that results in one or more of the following conditions: anemia, thrombocytopenia, bone disease, hepatomegaly or splenomegaly (15, 16). However, Cerezyme® is limited by its inability to treat type 2/3 Gaucher's disease, as it cannot cross the blood–brain barrier and due to its inherently inconvenient i.v. mode of administration. Although the safety profile is acceptable, Cerezyme® is associated with mild and transient adverse events, as well as antibody formation in a small proportion of patients (17).

A new ERT option for patients with type 1 Gaucher's disease is currently under development. Gene-Activated™ human glucocerebrosidase (velaglucerase alfa, GA-GCB) is human β-glucocerebrosidase (GCB), a glycoprotein produced from a well-characterized, continuous human cell line, that is produced by Shire Human Genetic Therapies using proprietary gene activation technology (18). Pharmacokinetic data from an open-label study in 12 type 1 Gaucher's disease patients have confirmed linear parameters over clinically relevant doses (15-60 U/kg by 1-h infusion), with results similar to other approved ERTs (19). Clinical activity has also been demonstrated in 36-month data presented from an ongoing phase I/II open-label study in 10 type 1 Gaucher's disease patients. Improvements in hemoglobin levels, blood counts and organ volumes were achieved at 60 U/kg and maintained with a dose reduction to 30 U/kg. No drug-related adverse events have been reported to date, with mild to moderate adverse events recorded in the majority overall (20). Three phase II/III clinical trials are currently ongoing in type 1 Gaucher's disease patients (21-23), with another phase III study undertaking a comparative investigation versus Cerezyme® (24). Long-term safety investigations are also ongoing in a phase I/II study (25).

Substrate inhibition therapies

More recently, miglustat (Zavesca®; Actelion Pharmaceuticals) has been approved as a treatment option for Gaucher's disease in the E.U., U.S., Canada, Switzerland, Turkey, Brazil, Australia and Israel (26). In contrast to ERTs, miglustat targets the substrate glucocerebroside (the substance that builds up in the cells and tissues of people with Gaucher's disease), and is therefore known as a substrate inhibition therapy (SIT). A dose of 100 mg is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher's disease, and may only be used in those patients for whom ERT is unsuitable (27). Actelion Pharmaceuticals is currently pitching miglustat as a promising maintenance therapy for type 1 Gaucher's disease (28). An open-label, noncomparative, multicenter phase III study to evaluate the long-term efficacy, safety and tolerability of miglustat as a maintenance therapy after a switch from ERT in adult patients with stable type 1 Gaucher's disease is currently ongoing (29).

A promising new SIT therapy for Gaucher's disease is GENZ-112638 (Genzyme), which has reached phase II clinical trials to date. GENZ-112638 is designed to partially inhibit GCase, which results in reduced production of glucosylceramide. Preclinical studies in Gaucher's disease mice (D409V-null) have confirmed that this agent is effective when given orally to prevent substrate accumulation and reduce it in established disease. Furthermore, phase I data have demonstrated a GENZ-112638-mediated inhibition of glucosylceramide in healthy volunteers at doses of 50 and 200 mg b.i.d. (30). Genzyme recently reported final results from a 52-week open-label phase II study, showing that 22 of 26 Gaucher's disease patients from North America, South America, Europe, Asia and the Middle East completed the full study period, with 91% of these patients demonstrating a clinically meaningful response in at least 2 of 3 primary endpoints (improvement in spleen size, hemoglobin and platelet levels). Furthermore, over 50% of patients have opted to stay on treatment for over two years. This study also revealed a promising safety profile, with only 9% of patients reporting mild, transient drug-related adverse events (infrequent abdominal discomfort and diarrhea, as well as transient palpitations and headache). These phase II studies are currently ongoing (31). Genzyme is also planning two phase III trials to investigate the efficacy of GENZ-112638 in untreated type 1 Gaucher's disease patients and in Gaucher's disease patients switching to GENZ-112638. These trials are expected to commence in mid-2009 (32).

Pharmacological chaperones

Pharmacological chaperoning is emerging as a novel treatment strategy for Gaucher's disease (33). This approach works by correcting the folding and trafficking of mutant GCase. The most promising candidate for Gaucher's disease to date is isofagomine (AT-2101; Amicus Therapeutics). Preclinical studies have shown that isofagomine selectively binds to misfolded GCase, increasing enzyme activity by 3.0 ± 0.6-fold via several mechanisms. After binding to the enzyme, it is thought that isofagomine promotes the proper folding, processing and trafficking of the enzyme from the endoplasmic reticulum to the lysosome at neutral pH. Once it reaches the lysosome, the pharmacological chaperone is displaced and the enzyme can perform its normal function (34-36). Isofagomine has completed a multicenter U.S. phase II study in patients with type 1 Gaucher's disease already receiving ERT (37), along with another clinical study to characterize the ex vivo response to therapy by testing blood samples from previously treated and untreated patients with Gaucher's disease (38). An additional multicenter phase II study is ongoing in the U.S., U.K., Germany and Israel to assess the safety and efficacy of isofagomine in patients with type I Gaucher's disease who are not receiving ERT or SRT (39).

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