Oral eliglustat maintains efficacy over 8 years in previously untreated adults with moderate to severe Gaucher disease type 1

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Video Abstract

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Abstract

A recently completed clinical trial of the oral drug eliglustat has delivered promising long-term results for adults with Gaucher disease type 1 – a rare and sometimes life-threatening genetic disorder that interferes with the breakdown of certain types of lipids. GD1 is caused by deficient activity of the lysosomal enzyme acid β-glucosidase. Reduced catalytic activity of the enzyme results in pathogenic accumulation of the enzyme's substrates, primarily glucosylceramide, in various organs. The result is progressive and debilitating enlargement of the spleen and liver, anemia, low platelet counts, and skeletal manifestations. The historical standard of care is biweekly intravenous infusions of recombinant enzyme, which boosts degradation of glucosylceramide. By contrast, eliglustat, an oral substrate reduction therapy, reduces glucosylceramide storage by slowing its production. Eliglustat was first approved in 2014 as a first-line treatment for adults with GD1 who have extensive, intermediate or poor cytochrome P450 2D6 metabolizer phenotypes. CYP2D6 phenotype, established through a blood test, determines how rapidly the drug will be metabolized and, by extension, the recommended dose. More than 90% of GD1 patients are eligible for eliglustat based on CYP2D6 phenotype. In this open-label Phase 2 trial, significant clinical improvements in previously untreated adults with moderate to severe GD1 were seen within 1 year. These improvements continued or were sustained over 8 years of eliglustat treatment. Mean spleen volume decreased by 69% (from 16.8 ± 9.5 to 4.9 ± 3.2 MN) and liver volume by 34% (from 1.7 ± 0.5 to 1.1 ± 0.3 MN). Hematologic measures also improved within 1 year, with a final improvement of 2.2 grams per deciliter for hemoglobin (from 11.3 ± 1.5 to 13.5 ± 1.2 g/dL) and 113% increase in platelet count (from 68.7 ± 21.2 to 135.3 ± 56.6 × 109/L). Mean lumbar spine bone mineral density T-scores increased by 0.96 (from −1.55 ± 1.05 to −0.59 ± 29), and mean femur bone mineral density T-scores increased by 0.21 (from 0.13 ± 0.69 to 0.33 ± 0.91) moving from the osteopenic range to the normal range. Gaucher disease biomarkers decreased markedly in parallel with clinical improvements. And quality of life measures, most of which were abnormal at baseline, normalized. The largest margins of improvement were found in patients with the most severe disease at baseline. These patients' final clinical parameters mirrored those with less severe disease at baseline, with all patient subgroups achieving mean values within established therapeutic goal thresholds for Gaucher disease. Eliglustat was generally well tolerated. Most adverse events were mild or moderate and not considered to be drug-related. And only 1 of 26 patients enrolled in the study withdrew due to an adverse event considered related to eliglustat. The study supports the use of eliglustat as a first-line treatment for adults with previously untreated GD1, including those with moderate to severe baseline disease.