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Encore! Oral therapy for type 1 Gaucher disease

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In this issue of *Blood*, Cox et al show that 157 adult patients with type 1 (nonneuronopathic) Gaucher disease (GD), whose initial signs and symptoms improved with biweekly IV infusions of pharmacologic recombinant glucocerebrosidase (enzyme replacement therapy [ERT]), remained stable for up to 4 years after switching to eliglustat tartrate, an oral inhibitor of glucocerebroside synthase (substrate reduction therapy [SRT]).[1] The study also demonstrated sustained normal values for validated patient-reported outcomes, including the Fatigue Severity Scale, the Brief Pain Inventory, and the 36-item short-form health-related quality of life instrument. This is important because wide discrepancies between GD response outcomes that are significant for patients and those most valued by physicians have been described.[2]

GD, an autosomal recessive hereditary disorder, is caused by deficient lysosomal acid–glucocerebrosidase activity. Its primary substrate, glucocerebroside (glucosylceramide) is one of the molecular building blocks of complex glycosphingolipids that are physiologically important constituents of cell membranes and receptor complexes. In the process of recycling senescent cells and other foreign elements, the lysosomes of glucocerebrosidase-deficient macrophages become engorged with glucocerebroside, glucosylsphingosine, and other bioreactive lipids that suppress osteoblast function and bone formation, cause immunologic dysregulation, and promote inflammation and hematologic B-cell malignancies, including myeloma.[3] Although type 1 GD is generally thought of as nonneuronpathic, even minor accumulation of glucocerebrosidase substrates may promote α-synuclein aggregation, attrition of dopaminergic neurons, and Lewy body formation and parkinsonism in 5% to 10% of elderly adult patients.[4]

Type 1 GD phenotypes are heterogeneous and only partly predictable by glucocerebrosidase gene sequencing. GD may present symptomatically at any age or sometimes remain undetected throughout life. At worst, GD is associated with massive hepatosplenomegaly, anemia, thrombocytopenia, and hemostatic defects. Bone manifestations, including acute pain crises, osteonecrosis, chronic bone pain, bone mineral loss, pathological fractures, and joint deformities, cause disability and impair quality of life. Untreated patients with progressive GD often die prematurely from bleeding complications, pulmonary hypertension, cirrhosis, sepsis, and even suicide. Many patients underwent total splenectomy with consequent exacerbation of debilitating bone disease.[5]

ERT is the gold standard treatment of GD. The 3 products currently approved in the United States, imiglucerase (1995), velaglucerase alfa (2010), and taliglucerase alfa (2012), differ slightly in amino acid structure and glycosylation, but are similar in terms of efficacy and safety. Exogenous glucocerebrosidase augments the attenuated activity of the patient's mutant glucocerebrosidase, thus restoring sphingolipid homeostasis[6] (see figure).

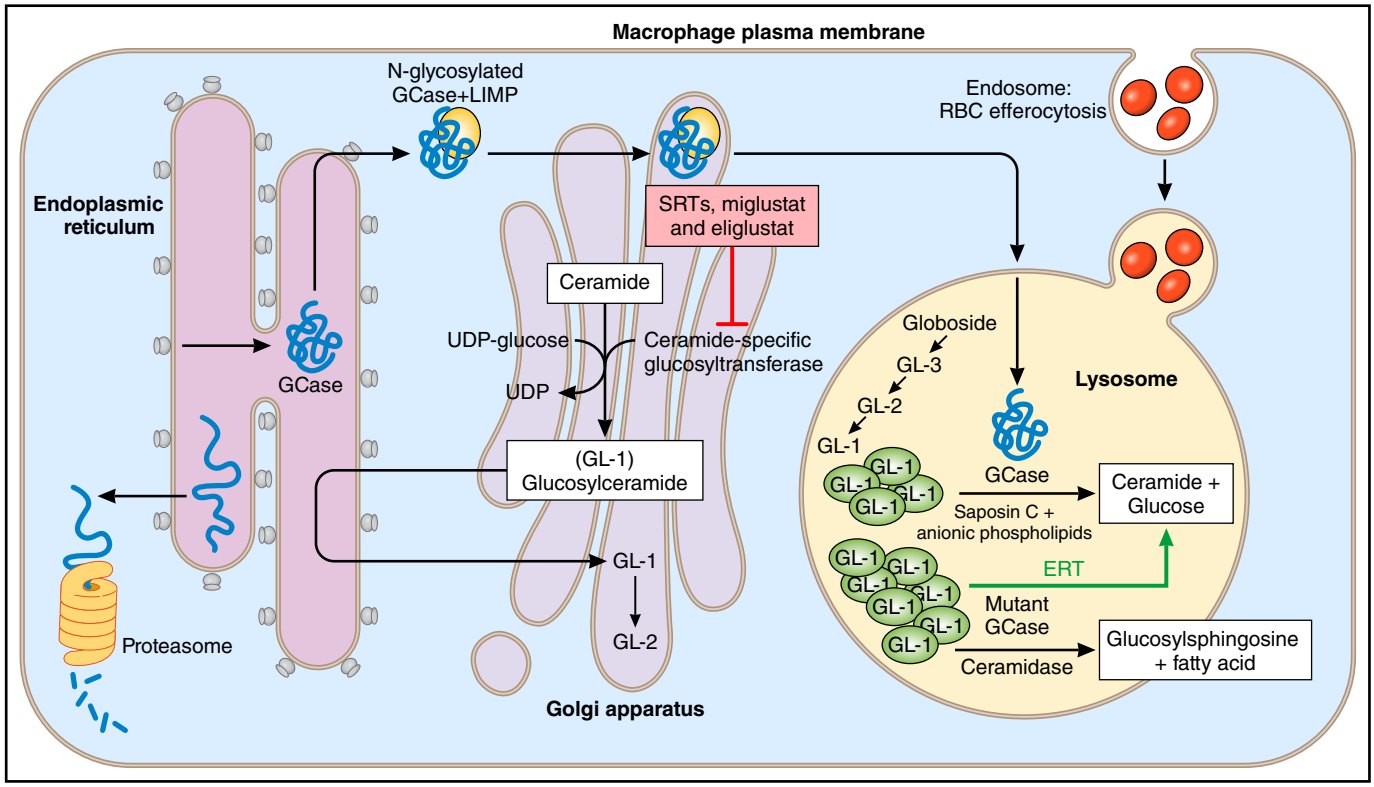
ERT (in a variable dose) is typically administered by IV infusion every 2 weeks. Within 1 to 2 years, anemia and hepatomegaly usually resolve, spleen volume decreases substantially, and thrombocytopenia generally improves. New bone crises are rare. Patients with chronic bone pain often experience some relief. Bone mineral density generally improves in children and younger adults. Patients report enhanced quality of life if they don't have preexistent irreversible bone disease. ERT has virtually obviated the need for splenectomy.[6]

Nonetheless, ERT has drawbacks. Lifelong IV treatments disrupt school, work, and travel, and venous access is often problematic. Up to 15% of ERT-treated patients develop antibodies that sometimes cause serious infusion reactions. Some patients continue to have persistent macrophage activation, elevated biomarkers, such as chitotriosidase and cytokines, and persistent bone marrow infiltration of Gaucher cells. Osteopenia and osteoporosis may not improve, especially in elderly patients, and new sporadic episodes of osteonecrosis and fracture may occur, especially in patients with a history of splenectomy. ERT is also ineffective for central nervous system (CNS) manifestations of neuronopathic GD.[7]

Because of these limitations, oral small molecule treatments with a wider tissue distribution than ERT were developed. Substrate reduction drugs retard synthesis of glucocerebroside by inhibition of ceramide-specific glucosyltransferase (see figure). The first approved SRT for GD, the iminosugar miglustat (2002), reversed hematologic and visceral manifestations in treatment-naive GD patients and, for 18 months, effectively maintained hemoglobin concentration and improved liver and spleen volumes in patients who had previously been on ERT. However, off-target GI side effects have prevented wide spread acceptance of miglustat by physicians and patients.[6]

Eliglustat tartrate, an oral ceramide analog, was approved by the US Food and Drug Administration in September 2014 for use in treatment-naive or ERT-treated adult GD patients with appropriate cytochrome P450 2d6 genotypes. The initial phase 2 trial and the phase 3 ENGAGE study that enrolled a combined 68 patients demonstrated that eliglustat is a safe and effective treatment for symptomatic treatment-naive adult patients with type 1 GD.[8] The ENCORE "switch and maintenance" trial, whose 4-year eliglustat open-label extension results are reported by Cox et al, is the largest randomized clinical trial so far attempted in patients with GD. Follow-up in most GD noninferiority studies is <2 years. During 2009 to 2011, when supply of imiglucerase was severely constrained, many patients remained clinically stable despite treatment interruptions and discontinuations. The observation that 46 ENCORE patients who switched to eliglustat remained stable for 4 years (and many others for at least 2 to 3 years) indicates a true drug effect.

The low number of eliglustat-related adverse events or unexpected side effects reported by



Glucocerebrosidase (GCase) is manufactured and *N*-glycosylated in the rough endoplasmic reticulum (ER) and folded by intracellular chaperones (ER Hsp70 family member BiP/Grp78) into a functional conformation. After association with lysosomal integral membrane protein (LIMP), GCase undergoes further processing and packaging in the Golgi apparatus and is delivered to the lysosome where, in association with an essential cofactor, saposin C, and anionic phospholipids, it catalyzes the hydrolysis of glucocerebroside (GL-1) to ceramide and glucose. Mutant GCases fail to properly fold in the ER and trigger the unfolded protein response, ubiquitination, and disassembly in the proteasome. However, some mutant GCase with variably residual hydrolytic activity does traffic to the lysosome. ERT is delivered directly to the lysosome where it augments the qualitatively and quantitatively deficient mutant GCase activity. GL-1 is synthesized de novo on the cytosolic surfaces of the Golgi and, via a detour to the smooth ER, is returned to the Golgi lumen where it is processed into more complex glycosphingolipids. SRTs slow the synthesis of GL-1 by the inhibition of ceramide glucsyltransferase. However, much of the GL-1 that is stored in Gaucher macrophages is derived exogenously, secondary to lysosomal degradation of senescent blood cells. Professional illustration by Patrick Lane, ScEYEnce Studios.

Cox et al is encouraging, but the history of statin side effects should be a sobering caveat. Evidence in this study that blood levels of bioactive lipids, such as ceramide and sphingomyelin, remained normal despite inhibition of glucosylceramide synthase is reassuring. However, blood levels may be an insensitive biomarker, and yet unrecognized SRT-induced perturbations in the flux of sphingolipids in subcellular organelles might be important positive or negative determinants of the safety of eliglustat and long-term patient outcomes, including malignancies and parkinsonism.[9] It should also be emphasized that because eliglustat is extruded from the CNS by P-glycoprotein, it is not a candidate for treatment of neuronopathic GD.

Bottom line: encore for a so far bravura performance, but will eliglustat be enduringly "fantastic" with prospective new treatment approaches, such as pharmacologic chaperones, biostasis modulators, and, ultimately, gene modification waiting in the wings?[10]

Conflict-of-interest disclosure: N.J.W. was a coinvestigator for the clinical trial that is reviewed (but not an author of the published manuscript) and has consulted, received honoraria for participation in scientific advisory boards, and received research grants from Genzyme, a Sanofi Company, the clinical trial sponsor, as well as honoraria and consulting fees from Shire HGT, Pfizer Corporation, and Actelion Corporation, all of whom manufacture and market treatments for type 1 Gaucher disease. ■

REFERENCES

1. Cox TM, Drelichman G, Cravo R, et al. Eliglustat maintains long-term clinical stability in patients with Gaucher disease type 1 stabilized on enzyme therapy. *Blood*. 2017;129(17):2375-2383.

2. Zion YC, Pappadopulos E, Wajnrajch M, Rosenbaum H. Rethinking fatigue in Gaucher disease. *Orphanet J Rare Dis*. 2016;11(1):53.

3. Mistry PK, Liu J, Sun L, et al. Glucocerebrosidase 2 gene deletion rescues type 1 Gaucher disease. *Proc Natl Acad Sci USA*. 2014;111(13):4934-4939.

4. Suzuki M, Fujikake N, Takeuchi T, et al. Glucocerebrosidase deficiency accelerates the accumulation of proteinase K-resistant α-synuclein and aggravates neurodegeneration in a Drosophila model of Parkinson's disease. *Hum Mol Genet*. 2015;24(23):6675-6686.

5. Weinreb NJ, Barbouth DS, Lee RE. Causes of death in 184 patients with type 1 Gaucher disease from the United States who were never treated with enzyme replacement therapy [published online ahead of print 24 October 2016]. *Blood Cells Mol Dis*. doi:10.1016/j.bcmd.2016.10.002.

6. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci*. 2017;18(2):E441.

7. Deegan PB, Pavlova E, Tindall J, et al. Osseous manifestations of adult Gaucher disease in the era of enzyme replacement therapy. *Medicine (Baltimore)*. 2011;90(1):52-60.

8. Mistry PK, Lukina E, Ben Turkia H, et al. Effect of oral eliglustat on splenomegaly in patients with Gaucher disease type 1: the ENGAGE randomized clinical trial. *JAMA*. 2015;313(7):695-706.

9. Abdul-Hammed M, Breiden B, Schwarzmann G, Sandhoff K. Lipids regulate the hydrolysis of membrane bound glucosylceramide by lysosomal β-glucocerebrosidase GBA1. *J Lipid Res*. 2017;58(3):563-577

10. Mistry PK, Lopez G, Schiffmann R, Barton NW, Weinreb NJ, Sidransky E. Gaucher disease: Progress and ongoing challenges. *Mol Genet Metab*. 2017;120(1-2):8-21.

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