Response to Letter to the Editor on “Enzyme Replacement or Substrate Reduction? A Review of Gaucher Disease Treatment Options”

Hospital Pharmacy
2017, Vol. 52(11) 727–728
© The Author(s) 2017
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/0018578717737135
journals.sagepub.com/home/hpx

Alison Van Rossum¹ and Megan Holsopple²

We appreciate the comments by Ibrahim and Call on our article “Enzyme Replacement or Substrate Reduction? A Review of Gaucher Disease Treatment Options,” particularly regarding information published since our article was originally written such as the extension study of the ENCORE trial.

In the ENCORE extension study, 147 patients with Gaucher disease type 1 were either continued on eliglustat (received up to 4.5 years of eliglustat therapy) or transitioned from imiglucerase to eliglustat (received 2 years of eliglustat therapy). At the end of the study, $\geq 85\%$ of patients maintained stable hematologic and organ volume values compared with baseline (pre-eliglustat) values. Adverse events were recorded in 94% of patients; the majority of the reported adverse events were considered mild (74%), and 8% of patients withdrew due to treatment-related adverse effects.¹

The ENGAGE trial was originally excluded because the authors chose to emphasize trials with an active comparator when possible. However, it is helpful to note that the ENGAGE trial demonstrated in 40 treatment-naïve patients with Gaucher disease type 1 that eliglustat reduced spleen volume by 27.77% after 9 months of therapy while spleen volume increased by 2.26% at 9 months in the placebo group (difference of -30.03% ; 95% confidence interval, -36.82% to -23.24% ; $P < 0.001$).² Similarly, a small trial evaluating miglustat in treatment-naïve patients was not included in the initial article. In the observational trial of 26 patients with Gaucher disease type 1, 10 of whom were treatment-naïve, miglustat showed significant changes from baseline in treatment-naïve patients in total cholesterol (7% increase; $P = 0.05$), high-density lipoprotein cholesterol (24% increase; $P = 0.005$), triglycerides (20% decrease; $P = 0.05$), C-reactive protein (32% decrease; $P = 0.05$), and chitotriosidase (39% decrease; $P = 0.03$) after 36 months of therapy. Other markers of Gaucher disease severity were not measured, and adverse effects were not discussed extensively.³

Regarding the note on antibody development, Ibrahim and Call are correct in stating there are no head-to-head trials between the enzyme replacement therapies and antibody development. In the initial article, we referred to the reported rates of antibody development to each of the agents. Currently, some published data report the rate of immunoglobulin G (IgG) antibody development to imiglucerase as

15%, IgG antibody development to taliglucerase as 6%, and IgG antibody development to velaglucerase as 1.4%.⁴⁻⁶ However, it is important to note that different resources will likely report different rates of antibody development and rates may not be directly comparable. In addition, as with any biological therapy, immunogenicity is a concern, and providers should monitor patients for signs and symptoms of immunologic responses.

We additionally acknowledge that reports of imiglucerase use in pregnancy women indicate imiglucerase may be a safe option for Gaucher disease treatment during pregnancy and may decrease the risk of complications in these patients during pregnancy.⁷ Similarly, reports and clinical experience suggest velaglucerase and taliglucerase may be safely used to treat Gaucher disease during pregnancy.^{7,8} However, while clinical experience with enzyme replacement therapy suggests these agents may be safe to use in pregnancy, enzyme replacement therapies, like most medications, have not been evaluated in pregnant women with adequate, well-controlled trials; therefore, safety cannot be guaranteed in this population. As noted in the original article, because imiglucerase has been on the market longest and thus has the longest history of clinical use, it may be a safer option than the newer enzyme replacement therapies.

Regarding the note on Canadian and European indications for taliglucerase and imiglucerase, the intent of our article was to address indications approved by Food and Drug Administration (FDA) for use in the United States. Of note, while the official indication approved by FDA for all 3 enzyme replacement therapies specifically states they are indicated for use in Gaucher disease type 1, FDA-designated imiglucerase as an orphan drug for Gaucher disease types 1, 2, and 3 and taliglucerase and velaglucerase have an orphan drug designation for Gaucher disease without specifying type.^{4,9-11} We encourage readers

¹University of Florida Health Jacksonville, FL, USA

²Froedtert & the Medical College of Wisconsin, Milwaukee, WI, USA

Corresponding Author:

Alison Van Rossum, University of Florida Health Jacksonville,
655 W 8th Street, Jacksonville, FL 32209, USA.
Email: alison.vanrossum@jax.ufl.edu

using these medications outside the United States to review approved uses in their country or region of practice. In addition, while knowledge of clinical use in other parts of the world may be beneficial in considering patient therapy options, it is also important to consider potential cost and reimbursement issues associated with using medications off-label. Insurance companies may not provide coverage for agents used outside the approved indications which could be detrimental to patient financial health.

We also appreciate the comments on treatment goals and Table 1: Gaucher disease characteristics by condition type. The information on prevalence and incidence provide updated data which have been published since the time our initial article was written. The additional comments provide insight into differences in the available published literature.

Finally, regarding the notes on recommended dosing and CYP2D6 ultrarapid metabolizers, we acknowledge that not all patients will have an appropriate response to standard doses and typical agents. The intent of the article was to provide general guidance for the majority of patients. However, like most pharmacologic therapies, medication choice and dosing should be selected based on individual patient characteristics, needs, and preferences. Clinical judgment should be used, and some patients may require therapy outside the typical treatment parameters.

References

1. Cox TM, Drelichman G, Cravo R, et al. Eliglustat maintains long-term clinical stability in patient with Gaucher disease type 1 stabilized on enzyme therapy. *Blood*. 2017;129:2375-2383.
2. Mistry PK, Lukin 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;313:695-706.
3. Puzo J, Alfonso P, Irun P, Gervas J, Pocovi M, Giraldo P. Changes in the atherogenic profile of patients with type 1 Gaucher disease after miglustat therapy. *Atherosclerosis*. 2010;209:515-519.
4. *CEREZYME-Imiglucerase Injection, Powder, Lyophilized, for Solution [package insert]*. Cambridge, MA: Genzyme Corporation; 2017.
5. Zimran A, Brill-Almon E, Chertkoff R, et al. Pivotal trial with plant cell-expressed recombinant glucocerebrosidase, taliglucerase alfa, a novel enzyme replacement therapy for Gaucher disease. *Blood*. 2011;118(22):5767-5773.
6. Pastores GM, Turkia HB, Gonzalez DE, et al. Development of anti-velaglucerase alfa antibodies in clinical trial-treated patients with Gaucher disease. *Blood Cells Mol Dis*. 2016;59:37-43.
7. Elstein D, Hughes D, Goker-Alphan O, et al. Outcome of pregnancies in women receiving velaglucerase alfa for Gaucher disease. *J Obstet Gynaecol Res*. 2014;40:968-975.
8. Elstein D, Rosenbaum H, Chertkoff R, Zimran A. Taliglucerase alfa during pregnancy for patients with type 1 Gaucher disease. *Mol Genet Metab*. 2016;117:S44.
9. *ELELYSO (Taliglucerase Alfa) Injection, Powder, Lyophilized, for Solution*. New York, NY: Pfizer Laboratories; 2017.
10. *VPRIV (Velaglucerase Alfa) Injection, Powder, Lyophilized, for Solution*. Lexington, MA: Shire US Manufacturing, Inc; 2016.
11. Food and Drug Administration. *Cumulative List of Orphan Drugs Designated and/or Approved*. Rockville, MD: Food and Drug Administration; 2017.