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Letter to the Editor

Miglustat Does Not Prevent Neurological Involvement in Niemann Pick C Disease

To the Editor:

Niemann Pick type C is a rare neurodegenerative lysosomal disease. In 2012, we reported the result of miglustat therapy in a girl treated from the age of 7 months and in a boy treated from the age of 16 months, both treated when neurologically asymptomatic.[1]

In the past 3 years, the now 10-year-old girl developed a cherry red spot, unusual in Niemann Pick type C, vertical gaze paralysis, ataxia, dysmetria, cataplexy during laughter, and significant cognitive decline requiring special teaching program. Her electroencephalograph is still normal.

The second child, now aged 9 years, developed mild decline of cognitive abilities, hyperreflexia, and mild incoordination, but not gaze paralysis. His electroencephalograph is normal.

Both patients started the treatment with miglustat assuming that if miglustat stabilizes motor function and improves swallowing and saccadic eye movement in patients already showing neurological impairment at baseline,[2] then it could prevent neurological impairment when started in neurologically asymptomatic patients.

Our experience seems to show that miglustat does not prevent the neurological involvement even if started very early and raises the question about its efficacy in Niemann Pick type C. Moreover, postmarket studies, when long-lasting enough, demonstrated that some Niemann Pick type C patients worsened and/or died after an initial period of stabilization.[3]

Inefficacy of miglustat could be explained by the fact that it acts by reducing the storage of sphingosine, which is one of consequences of Niemann Pick type C mutation/inactivation; in fact, the pathogenic cascade includes the storage of multiple lipids, defective lysosomal calcium homeostasis, block in late endosome-lysosome fusion, impaired autophagy, mitophagy, and neuroinflammation.[4]

Miglustat was approved for Niemann Pick type C in Europe in 2009, in Canada in 2010, and in Japan in 2012. But in United States, the Food and Drug Administration declined to approve it in 2010 and required additional preclinical and clinical information. By reporting these two children, we would like to focus on a crucial problem: some orphan drugs are approved with limited premarket studies, a small number of participants, lack of blinding or randomization, and lack of knowledge about natural history of the disease; furthermore, sometimes end points of the studies are irrelevant in comparison to the burden of the disease.

Thus patients with rare diseases may have a greater likelihood of ineffective therapies compared with patients with more common diseases.[5] Finally, we need to make clear to patients with rare diseases and their families that ineffective drugs should be stopped or not started, countering the argument that an ineffective orphan drug is better than no drug.

References

1. Di Rocco M, Dardis A, Madeo A, Barone R, Fiumara A. Early miglustat therapy in infantile Niemann-Pick disease type C. *Pediatr Neurol*. 2012;47:40-43.
2. Patterson MC, Vecchio D, Prady H, Abel L, Wraith JE. Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. *Lancet Neurol*. 2007;6:765-772.
3. Fecarotta S, Romano A, Della Casa R, et al. Long term follow-up to evaluate the efficacy of miglustat treatment in Italian patients with Niemann-Pick disease type C. *Orphanet J Rare Dis*. 2015;10:22.
4. Vanier MT. Complex lipid trafficking in Niemann-Pick disease type C. *J Inherit Metab Dis*. 2015;38:187-199.
5. Kesselheim AS. Ethical considerations in orphan drug approval and use. *Clin Pharmacol Ther*. 2012;92:153-155.

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