

Treatment with Miglustat in Patients Suffering from NPC

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Niemann-Pick disease type C (NPC) is a rare autosomal recessive, lysosomal storage disease characterized by impaired intracellular lipid trafficking leading to accumulation of cholesterol and glycosphingolipids in various tissues. NP-C is characterized by visceral, neurological, and psychiatric manifestation.

Until recently, there was no curative treatment for NP-C; management remains mainly supportive and symptomatic treatment to improve health-related quality of life (HRQOL). Now the disease-specific treatment approved. The aims of the treatment are to stabilize or slow disease progression.

Miglustat (N-butyldeoxynojirimycin; NB- DNJ; Zavesca) is the only disease-specific oral therapy approved to treat progressive neurological manifestation of NP-C. Iminosugar molecule reversibly inhibits glycosphingolipid synthesis. It has beneficial effects on lipid trafficking defects, reducing the neurotoxic accumulation of glucosylceramide, lactosylceramide, and gangliosides GM2 and GM3 in the brain and delaying the progression of neurological symptoms of NP-C but it has no effect on the systemic manifestations.

NBDNJ appears to have pleotropic effects in humans, as demonstrated by its ability to reduce GSL accumulation and inflammation. Nevertheless, it has the potential adverse molecular effects on cellular processes, including signalling protein localization. It causes reduced conduction velocity and myelination, axonal degeneration, and increases susceptibility to excitotoxicity. Ganglioside reduction and substrate deprivation by NBDNJ treatment is a more viable treatment in humans because the drug does not result in permanent depletion of the ganglioside reserves.

Miglustat should be started immediately at the earliest sign of neurological manifestation. The recommended dose of miglustat for the treatment of patients 12 years of age and above is

200mg three times a day and dosing in patients under the age of 12 years should be adjusted based on body surface area. The most common adverse effects associated with miglustat treatment are gastrointestinal with mild to moderate diarrhea, vomiting, flatulence, and weight loss tending to decrease over time.

For patients whose diagnosis is based on sibling screening or systemic manifestation of NP-C with initiation of miglustat at the first neurological sign, the response is generally better. There is very limited data of effective of treatment with miglustat to prevent neurological symptoms for asymptomatic patients.

Keywords: Treatment; Miglustat; NPC

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