

New therapies in the management of Niemann-Pick type C disease: clinical utility of miglustat

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Abstract: Niemann-Pick disease type C (NP-C) is an autosomal recessive disorder characterized by progressive neurological deterioration leading to premature death. The disease is caused by mutations in one of two genes, *NPC1* or *NPC2*, leading to impaired intracellular lipid transport and build-up of lipids in various tissues, particularly the brain. Miglustat (Zavesca®), a reversible inhibitor of glycosphingolipid synthesis, has recently been authorized in the European Union, Brazil and South Korea for the treatment of progressive neurological symptoms in adult and pediatric patients, and represents the first specific treatment for NP-C. Here we review current data on the pharmacology, efficacy, safety and tolerability of miglustat in patients with NP-C, based on findings from a prospective clinical trial, preclinical and retrospective studies, and case reports. Findings demonstrated clinically relevant beneficial effects of miglustat on neurological disease progression in adult, juvenile and pediatric patients with NP-C, particularly those diagnosed in late childhood (6–11 years) and in juveniles and adults (12 years and older), compared with those diagnosed in early childhood (younger than 6 years). Miglustat therapy was well-tolerated in all age groups. With the approval of miglustat, treatment of patients with NP-C can now be aimed toward stabilizing neurological disease, which is likely the best attainable therapeutic goal for this disorder.

Keywords: Niemann-Pick disease type C, NP-C, miglustat, Zavesca®

Introduction

Niemann-Pick disease type C (NP-C) is a rare, panethnic, autosomal recessive disease with an incidence estimated at between 1:120,000 and 1:150,000 live births.^{1–3} NP-C is characterized by progressive neurological deterioration leading to premature death. The disease is caused by mutations in either one of two genes, *NPC1* or *NPC2*. *NPC1* gene mutations are present in 95% of cases, and *NPC2* mutations are present in approximately 4%.^{4–7} The remainder of patients are biochemically-proven cases who do not have identified mutations.

Mutations in *NPC1* and *NPC2* give rise to severe abnormalities in the intracellular transport of lipid, notably cholesterol, glycosphingolipids and sphingosine.^{8–12} The *NPC1* or *NPC2* gene products normally function cooperatively in intracellular lipid transport,^{8,13,14} and so impaired function leads to the accumulation of lipids in the late-endosomal and lysosomal intracellular compartments, resulting in the build-up of excess lipids in various tissues. In the liver and spleen, excess storage of unesterified cholesterol, sphingomyelin, bis(monoacylglycerol)phosphate, glycosphingolipids and sphingosine can lead to visceral symptoms such as organomegaly and liver dysfunction,^{15–18} while increased levels of glucosylceramide, lactosylceramide, and particularly G_{M2} and G_{M3}

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gangliosides in the brain could contribute to the neurological manifestations of the disease.¹⁹

NP-C has an extremely heterogeneous clinical presentation characterized by a wide range of symptoms that are not specific to the disease, and which arise and progress over varied periods of time.^{1,7} Presenting manifestations differ according to the individual patient and are heavily dependent on the patient's age at the onset of disease. Diagnosis can therefore be difficult and is often delayed by several years after presentation of the first symptoms. A clinical diagnosis of NP-C requires in-depth screening for characteristic neurological (as well as systemic) features, and must be confirmed by laboratory biochemical and/or molecular genetic testing.^{1,3} The key laboratory diagnostic test for NP-C is filipin staining of cultured skin fibroblasts from the patient, to demonstrate free cholesterol accumulation in lysosomes secondary to impaired intracellular cholesterol transport.²⁰ Evaluation of the rate of intracellular cholesterol esterification is a useful complementary test.²⁰ Molecular genetic testing for *NPC1* and *NPC2* gene mutations is also vital to confirm diagnoses in patients with a variant biochemical phenotype, as well as to enable early and reliable prenatal diagnosis.²⁰

Until recently, treatment for NP-C has been limited to supportive measures, for relief of specific manifestations of the disease. Anti-epileptics to control seizures, antidepressants for treatment of cataplexy and anticholinergics to control tremor and dystonia may all be employed to help improve the quality of life of NP-C patients.^{3,21,22} Systemic manifestations, such as gastrointestinal symptoms can be managed with anti-diarrheal medications, and simple measures such as softening of food for patients with dysphagia can also be beneficial.³

A number of experimental disease-specific therapies, based on the molecular pathology of NP-C, have been tested in cell culture and animal models. These include neurosteroids and cholesterol-binding agents, which have been shown to delay the progression of disease in animal models of NP-C.^{23–25} Direct or indirect overexpression of the GTPase, Rab 9, has been shown to reverse the NP-C phenotype in tissue culture^{26,27} and reduce stored lipids and prolong lifespan in a mouse model of NP-C.²⁸ Recently, curcumin has been suggested to have beneficial effects on intracellular calcium homeostasis and lipid metabolism in *NPC1*-mutant mice.²⁹ However, data from clinical studies are required to assess the possible role of these compounds in NP-C therapy.

Miglustat (Zavesca®; Actelion Pharmaceuticals Ltd, Allschwil, Switzerland) is the first and only approved therapy for patients with NP-C. Miglustat is a small iminosugar

molecule that reversibly inhibits glycosphingolipid synthesis.³⁰ Miglustat is approved in the European Union (EU), USA, Canada, Brazil, Australia, Turkey, Israel, Switzerland, South Korea and New Zealand for the treatment of patients with mild to moderate type 1 Gaucher disease (GD1) for whom enzyme replacement therapy (ERT) is unsuitable or not a therapeutic option. Recently, the EU Commission extended miglustat's indication to include the treatment of progressive neurological manifestations in adult patients and pediatric patients with NP-C. This was followed by authorization in Brazil and South Korea. These approvals were based on findings from preclinical studies, a prospective clinical trial and a retrospective cohort study. Here we review the current literature on the pharmacology, efficacy, safety and tolerability of miglustat in NP-C.

Neurological manifestations in NP-C

Both the symptomatology and the rate of disease progression of NP-C are heavily influenced by the age of the patient at the onset of disease.^{1,3,31–33} In neonates and infants, NP-C typically manifests as organomegaly and severe liver dysfunction, while later onset forms are primarily neurological in nature. In late infantile-onset patients, NP-C typically presents as ataxia, cognitive impairment and clumsiness. Impaired vertical saccadic eye movements are invariably present, but are often overlooked. Gelastic cataplexy and epileptic seizures are also common; progressive dystonia, dysphagia and dysarthria manifest as the disease advances.^{34–36} These manifestations also feature in juvenile- or adult-onset disease; however learning disabilities (often leading to school failure), behavioral problems, psychiatric signs and slowly-progressive motor problems are also common in these age groups.^{3,31,33,37,38} Cognitive impairment and dementia are most commonly seen in adult-onset patients.

In an observational retrospective study of the natural history of neurological disease in 57 patients with NP-C,³¹ patients were assessed using a modified version of an NP-C specific disability scale,³² which rated the severity of defects in ambulation, manipulation, language and swallowing. Overall, the rate of neurological deterioration was similar across all four measures. However, progression of neurological disease was consistently more rapid in patients who were diagnosed during early childhood (younger than 6 years), compared with those diagnosed in late childhood (6 to 11 years) or with juvenile or adult presentation (12 years or older)³¹ (Figure 1). Similarly, studies of patients with NP-C in the UK and Spain have

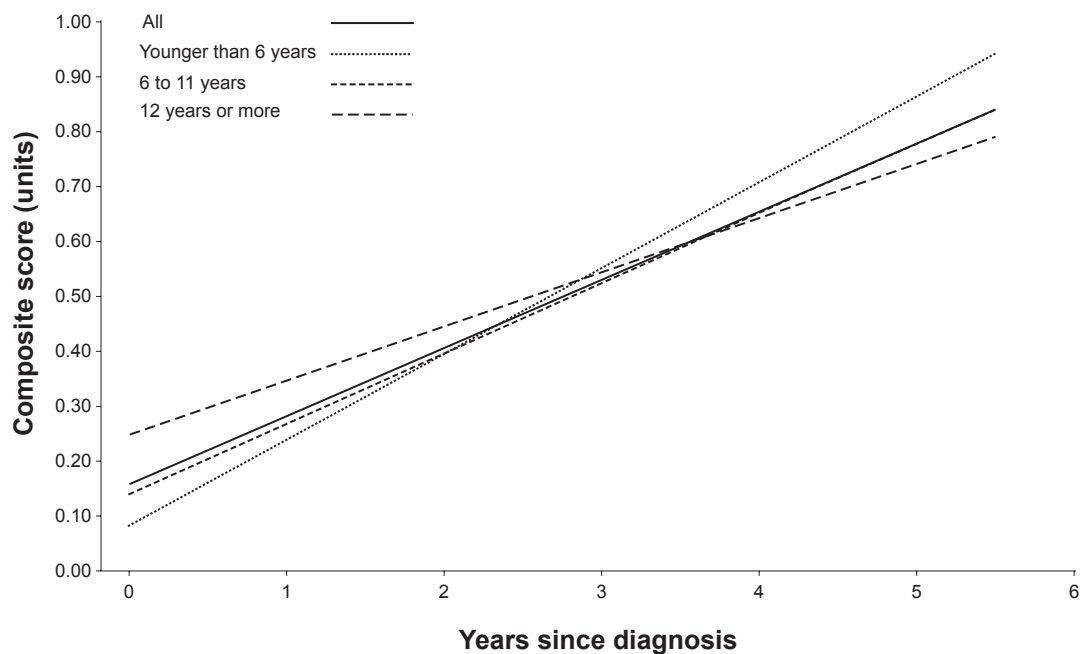


Figure 1 Change in composite disability score over time for overall NP-C population ($n = 57$) and by age at diagnosis group (untreated patients). Reproduced with permission from Wraith JE, Guffon N, Rohrbach M, et al. Natural history of Niemann-Pick disease type C in a multicentre observational retrospective cohort study. *Mol Genet Metab.* 2009;98:250–254.³¹ Copyright © 2009 Elsevier.

also indicated a more rapid progression of disease and early death in patients with early-onset NP-C, and slower, more subtle progression in juvenile- and adult-onset patients.^{32,33} A study in patients with NP-C in the US has also recently demonstrated linear disease progression, but did not detect a link between age of onset and the rate of progression.³⁷ This was likely due to the small size and varied nature of the patient cohort, which had very few juvenile or adult-onset patients. In addition, patients were undergoing various therapies during the study, which may have confounded the study results.

Since NP-C is primarily a neurological disease, at least in patients whose symptoms develop in early childhood or later, any effective treatment for NP-C needs to be able to cross the blood–brain barrier in order to prevent further neuronal damage. While the precise sequence of neuropathological changes leading to neurological disease progression in NP-C is not currently clear, it is considered likely that symptoms arise from two populations of brain cells: those that have been lost via cell death and those that are dysfunctional, but still viable. In either case, permanent neuronal damage will already have occurred by the time most patients are diagnosed with NP-C. One study has suggested that the appearance of clinical symptoms may indicate that overall neuronal impairment has reached a threshold level, and that pathological functional changes have become irreversible.³⁷ There is the possibility that certain symptoms of NP-C could

be associated with dysfunctional (but still living) cells. However, given the vast heterogeneity of neuropathologies and clinical neurological manifestations in NP-C, it is not currently considered possible to discern whether changes (improvement or deterioration) in certain symptoms may be related to direct therapeutic effects on subpopulations of brain cells, or just a product of patient-to-patient variability. Overall, experts agree that in most patients with NP-C, stabilization of neurological disease is likely the best attainable therapeutic goal.³ Therapeutic benefits with miglustat in NP-C are therefore considered in terms of delaying or halting the progression of neurological manifestations of NP-C.

Due to the heterogeneous nature of neurological manifestations in NP-C, the choice of clinical endpoints and monitoring techniques is vast. So far, no clinical tools have been validated for monitoring disease progression in patients with NP-C; nevertheless, clinical studies are a source of valuable information on which assessment measures may have the most clinical utility. The functional disability scale used by Iturriaga et al³² and modified for the observational study of neurological disease progression in NP-C,³¹ incorporates four parameters of disease that are clinically relevant across all age groups that typically experience neurological manifestations, and is a simple, easy-to-use instrument for the assessment of progression of neurological disease. Although it has yet to undergo formal validation studies, the scale has been shown to be capable of detecting differences in severity

and progression rates between different age subgroups of patients with NP-C.^{31,32}

One limitation of the functional disability scale is that it does not capture psychiatric symptoms; for patients with psychiatric impairment, various neuropsychiatric evaluations are available, including the Mini-Mental State Examination (MMSE) as a general measure of cognition,³⁹ and the Frontal Assessment Battery (FAB),⁴⁰ which evaluates cognitive domains that are most commonly affected in NP-C, particularly late-stage patients with predominantly frontal dementia. Magnetic resonance imaging (MRI) may also be a useful measure for detecting these late changes, particularly for the detection of cerebellar atrophy in later stages of disease. In addition, proton magnetic resonance spectroscopic imaging (H-MRSI), by evaluation of choline/creatine ratios, has been proposed as a more sensitive imaging technique to monitor disease progression in NP-C.⁴¹

As supranuclear gaze palsy is a common neurological manifestation of NP-C that occurs across the age groups, ophthalmic measures, such as saccadic eye movement (SEM), have been employed to measure the effect of treatment on neurological manifestations in patients with NP-C.⁴² Specialized assessments of SEM can be conducted based on video-recorded eye movements, and subsequent computerized measurements of peak velocity, amplitude and duration of either or both of horizontal or vertical eye movements. However, the clinical validity of SEM data has been questioned; there is some debate over whether these measures are related to overall disease severity, as they do not always correlate with other clinical parameters.⁴³ SEM data may therefore not fully detect clinical benefit from treatment in patients with NP-C.

Pharmacology and pharmacokinetics of miglustat

Mode of action

Miglustat is a small iminosugar molecule that acts as a competitive inhibitor of the enzyme glucosylceramide synthase, which catalyzes the first committed step in glycosphingolipid (GSL) synthesis, the glycosylation of ceramide.³⁰ This inhibits the synthesis of all glucosylceramide-derived glycosphingolipids. The inhibition of GSL synthesis by miglustat has been demonstrated to reduce pathological intracellular lipid storage, improve fluid-phase endosomal uptake and normalize lipid transport in peripheral blood B lymphocytes of NP-C patients.⁴⁴ This leads to a reduction of the potentially neurotoxic accumulation of gangliosides G_{M2} and G_{M3} , lactosylceramide and glucosylceramide, and may

prevent further neuronal damage. This is thought to be the primary mode of action of miglustat in NP-C.

Recent studies have suggested that miglustat indirectly modulates intracellular calcium homeostasis through its effects on glucosylceramide levels.⁴⁵ There is evidence to suggest that impaired calcium homeostasis related to sphingosine storage may be an initiating factor in the pathogenesis of NP-C.²⁹ Sphingosine accumulates in the lysosomes of *NPCI*-mutant cells, and this is thought to inhibit lysosomal calcium uptake, as demonstrated in a study using human and mouse *NPCI*-mutant cells.²⁹ Depletion of lysosomal calcium leads to impaired endocytic function and subsequent lipid storage, thus inducing the NP-C disease phenotype. The effect of miglustat on intracellular calcium levels might therefore influence an important underlying pathogenetic mechanism of NP-C.

Pharmacokinetics

The pharmacokinetics of miglustat have not been assessed in patients with NP-C, but are likely to be similar to those seen in patients with GD1. In patients with GD1, miglustat is rapidly absorbed after oral administration; the time taken to reach maximal plasma drug concentration (t_{max}) is approximately 2 to 2.5 hours. The absolute bioavailability of miglustat is at least 80%. Although taking miglustat with a fatty meal can extend t_{max} , this effect is not considered clinically relevant. The pharmacokinetics of miglustat in GD1 are approximately dose-proportional,^{46, 47} and the mean volume of distribution is large, at around 83 to 105 L. This indicates that miglustat is not restricted to the bloodstream, and can distribute into extravascular tissues.⁴⁷ Data from animal studies have confirmed that miglustat has specific physico-chemical properties (including lipid solubility and electrical charge) that allow wide tissue distribution, and the ability to cross the blood-brain barrier.⁴⁸ This wide tissue distribution is essential to enable miglustat to reach all of the affected body tissues and organs in NP-C, particularly the brain.

Although miglustat can penetrate the blood-brain barrier, concentrations of the drug in the cerebrospinal fluid are lower than plasma levels. To compensate for this, a higher dose than the 100 mg 3 times daily recommended in GD1, which is primarily a systemic disease, is required for patients with NP-C. A dose of 200 mg three times daily was therefore selected for adult patients, which should be reduced in proportion to body surface area in pediatric patients. The three-times-daily dosing regimen is a result of the fact that miglustat remains in the body for around 8 hours, and must therefore be taken three times daily to maintain therapeutic

levels. Miglustat is not metabolized *in vivo*, and so has a low mean rate of clearance from the body (mainly via the kidneys) of 11.8 to 13.8 L/hour.⁴⁷ The half-life of miglustat of 6 to 7 hours predicts that steady-state conditions will be achieved soon after treatment initiation. In clinical studies of miglustat in patients with GD1, steady-state was reached after 4 to 6 weeks of treatment.⁴⁹

Effects of miglustat in animal models of NP-C

The discovery that miglustat has the ability to cross the blood–brain barrier and reduce intracellular lipid storage in NP-C cell culture models led to a study of the effect of the drug in animal models of NP-C. In NP-C mice, only 11% of animals treated with miglustat developed an NP-C clinical phenotype after 50 to 62 days, while 78% of non-treated mice displayed the same manifestations.⁵⁰ By 65 to 78 days, all of the non-treated mice had developed symptoms of NP-C, compared with 56% of treated mice. Mean survival in treated mice was 89 days, compared with 67 days in untreated mice.⁵⁰ Cerebellar pathology and storage of G_{M2} and G_{M3} gangliosides were also shown to be reduced in the treated mice compared with those that did not receive treatment. These findings suggest that miglustat can delay the progression of NP-C and prolong survival. Similarly, in a feline model of NP-C, cats treated with miglustat showed a delay in the onset and progression of symptoms.⁵⁰ Ganglioside accumulation in the brain was also reduced.⁵⁰

Efficacy

Following positive results from preclinical and animal studies, a prospective, randomized clinical trial (OGT-918-007) was designed and implemented to assess the efficacy, safety and tolerability of miglustat in patients with NP-C. Juvenile or adult patients (aged 12 years or older) were enrolled, and randomized to either miglustat 200 mg three times daily ($n = 20$) or standard care ($n = 9$).⁴³ The randomized phase of the study was 12 months in duration. In parallel to this randomized trial, a pediatric sub-study assessed the effects of miglustat in children ($n = 12$) aged from 4 to 11 years with NP-C.^{43,51} These pediatric patients received open-label miglustat for 12 months at a dose adjusted for their body weight.

In adult and juvenile patients, improvements in the primary endpoint, horizontal saccadic eye movement peak velocity (HSEM- α) were seen in miglustat-treated patients *versus* those receiving standard care at Month 12, a finding that was statistically significant when patients receiving concomitant benzodiazepine therapy were excluded from

the analysis.⁴³ Benzodiazepines are known to impair saccadic eye movements. Benefits of miglustat therapy were also seen on measures of swallowing capacity, auditory acuity and ambulation. An overall mean improvement in HSEM- α was also seen in pediatric patients at Month 12.⁴³

Adult and juvenile patients who completed the randomized phase of the study were eligible to continue treatment in a 12-month, non-controlled extension phase. Following this, patients could enter a long-term ‘continued extension’ phase. Similarly, pediatric patients who completed the first 12 months were eligible to continue treatment for a 12-month extension period followed by a long-term ‘continued extension’ phase. Long-term data from the open-label extension phases have also been reported.⁵² In all patients who had at least one assessment during the continued extension phase (past 24 months, $n = 14$), swallowing capacity was improved in more than 75% patients. Median standard ambulation index scores indicated stabilization.⁵² A disease stability analysis of 19 adult or juvenile patients who completed at least 12 months of miglustat therapy, based on four key parameters of disease progression (HSEM- α , swallowing, ambulation and cognition), showed that 68% had stable disease after treatment (unpublished data Wraith et al 2009).

In pediatric patients, the overall mean improvement in HSEM- α velocity was maintained at Month 24, and stabilization of ambulation and swallowing was also achieved.⁵¹ The analysis of key parameters of disease progression revealed that 80% of pediatric patients who entered the extension phase had stable disease by Month 24, suggesting that miglustat provided similar benefits in pediatric patients as in juveniles and adults.⁵¹ These findings indicate that long-term miglustat therapy stabilizes neurological manifestations in pediatric, juvenile and adult patients with NP-C.

In addition to the prospective clinical trial, the effect of miglustat on the progression of neurological disease in patients with NP-C has been studied in an international, multicentre, observational cohort study. Sixty-six patients with NP-C treated with miglustat in clinical practice at 25 expert centers were assessed retrospectively⁵³ using a modified disease-specific disability scale.³² The scale analyzed four key parameters of neurological disease progression in NP-C: ambulation, manipulation, language and swallowing. The mean annual progression was +0.11 score units/year on the disability scale from diagnosis to treatment start, indicating considerable disease progression prior to initiation of miglustat therapy. Annual progression decreased to –0.01 score units/year from treatment start to the last clinic visit, indicating disease stabilization with miglustat therapy.

Previous epidemiological studies have established that NP-C tends to present in a range of different clinical forms defined by patients' age at onset of neurological symptoms: early-infantile (onset 3 months to <2 years), late-infantile (onset 2 to <6 years), juvenile (onset 6–15 years) and adult (onset >15 years).^{20,32,33,54} When the patients in the retrospective miglustat cohort were divided into three age groups, stabilization of neurological disease was observed in all groups. However, the magnitude of the effect was greater in patients diagnosed in late childhood (6–11 years) and in juveniles and adults (12 years and older), compared with those diagnosed in early childhood (younger than 6 years) (Figure 2).

The efficacy of miglustat in patients with NP-C has also been demonstrated in a number of case series.^{41,55,56} In two Taiwanese patients treated with miglustat for one year, cognitive improvement was observed in one patient and liver and spleen volumes and chitotriosidase levels were stabilized in both patients.⁵⁵ One patient had severe swallowing difficulties at baseline; this was greatly improved with miglustat treatment. The patient that showed improved cognition had a later disease onset (late childhood) compared with the second patient, whose presenting symptoms occurred in infancy. A report of a Brazilian patient with early childhood onset NP-C who received miglustat for 12 months indicated improvements in speech, ataxia, seizures, hypotonia, gaze

palsy and behavioral symptoms, and particularly ambulation.⁵⁶ Brain magnetic resonance spectroscopy was used to assess the effects of 24 months' miglustat treatment in three patients with NP-C. A decrease in choline/creatine ratio was identified as a potential marker for treatment efficacy, as a sustained decrease correlated with mild improvement or stabilization of clinical manifestations (swallowing, dysarthria, awareness or ambulation) achieved with miglustat therapy.⁴¹ The choline/creatine ratio is a measure of membrane destruction, or gliosis, so can be used as a marker for brain dysfunction.⁴¹ Together, these findings support data from the prospective clinical trial and observational cohort study, indicating beneficial therapeutic effects of miglustat in patients with NP-C.

Recommended clinical use of miglustat

An expert panel convened in Paris, France in January 2009 to discuss best care practices for NP-C. Recommendations on the management of NP-C patients based on consensus between the experts at the meeting were provided, including guidance on how to initiate miglustat therapy.³ The experts recommended that miglustat treatment should be started immediately in diagnosed patients with any type of neurological manifestations. Meanwhile, in patients who do not have neurological manifestations but for whom there is a known family history and

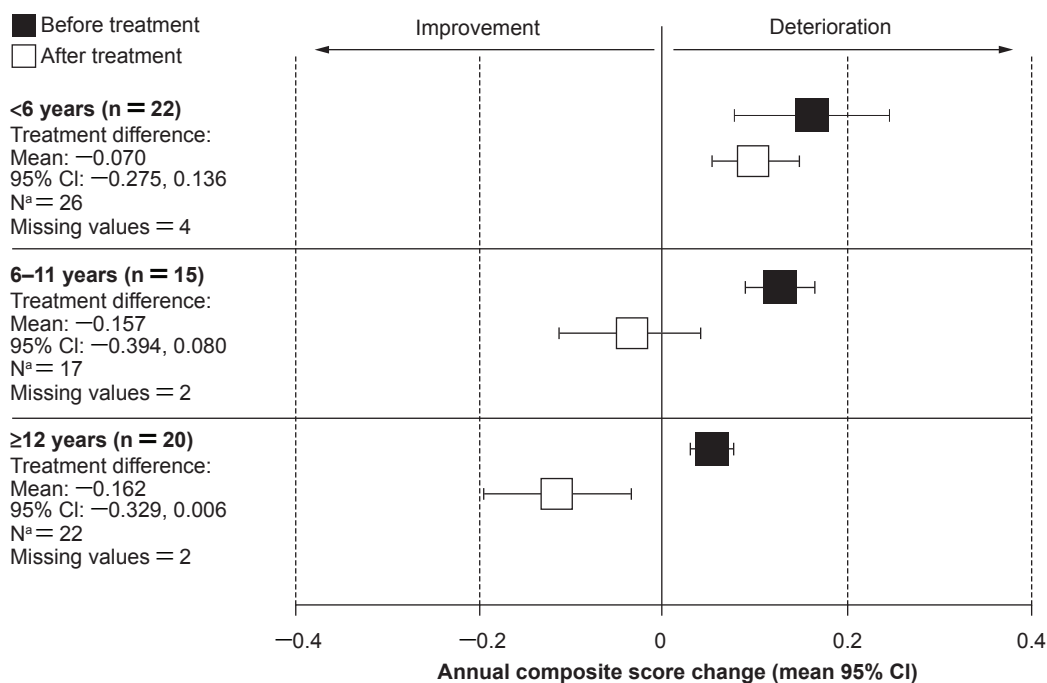


Figure 2 Annual changes in composite disability scores by age group in NP-C patients treated with miglustat. Reproduced with permission from Pineda M, Wraith JE, Mengel E, et al. Miglustat in patients with Niemann-Pick Type C disease (NP-C): a multicentre observational retrospective cohort study. *Mol Genet Metab.* 2009;98:243–249.⁵³ Copyright © 2009 Elsevier.

Note: ^aTotal number of patients per age group.

disease course, treatment should be commenced at or before the anticipated time of neurological symptom onset. However, patients with early-infantile onset NP-C, and those with severe dementia in the terminal stage of the disease, are less likely to benefit from treatment with miglustat and decisions to start treatment should be made on a case by case basis. Based on these guidelines, a protocol for the initiation of miglustat treatment in NP-C was developed (Figure 3).

The recommended dose of 200 mg three times daily for adult patients with NP-C should be adjusted according to body surface area for younger patients, as shown in Table 1.³ In general miglustat therapy should be continued as long as patients continue to derive discernable therapeutic benefits with an acceptable tolerability and safety profile. In early-infantile onset disease it can take up to 6 to 12 months to see discernable clinical benefits and 2 to 3 years in later-onset disease. Given the high variability of NP-C in terms of symptomatology and rate of progression, decisions to alter or discontinue treatment with miglustat should be based on individual patient characteristics, in consultation with the patient and their family members. In cases where there is a perceived lack of response, dose manipulation can be undertaken with careful consideration of risk versus benefit and patient tolerability.³

A disease-specific registry to evaluate the long-term disease course in patients with NP-C, both untreated and treated with

miglustat, has been designed by an international scientific committee⁵⁷ and will be implemented in late 2009. One of the objectives of this registry is to describe the natural history of NP-C and to evaluate the treatment experience of patients with NP-C, including the longitudinal assessment of outcomes. The registry will employ the functional disability scale³² to assess the progression of neurological disease. This first international registry for patients with NP-C will provide important further information on patient outcomes during miglustat therapy in real-world, clinical practice settings, and will bring together information from a larger number of patients.

Safety and tolerability

Findings from the prospective clinical trial demonstrated that miglustat has a similar safety and tolerability profile in pediatric and adult and juvenile patients with NP-C to that seen in patients with GD1.^{49,58,59} The most frequently reported treatment-emergent adverse events with miglustat therapy were mild or moderate diarrhea, flatulence and weight loss (Table 2).^{43,51} The incidence of gastrointestinal adverse events and mild to moderate weight loss tended to decrease over time on continued therapy. No deterioration of growth rates was noted in pediatric or juvenile patients treated with miglustat.⁵¹ Neurological adverse events such as tremor, headache and fatigue were also commonly reported, but were generally

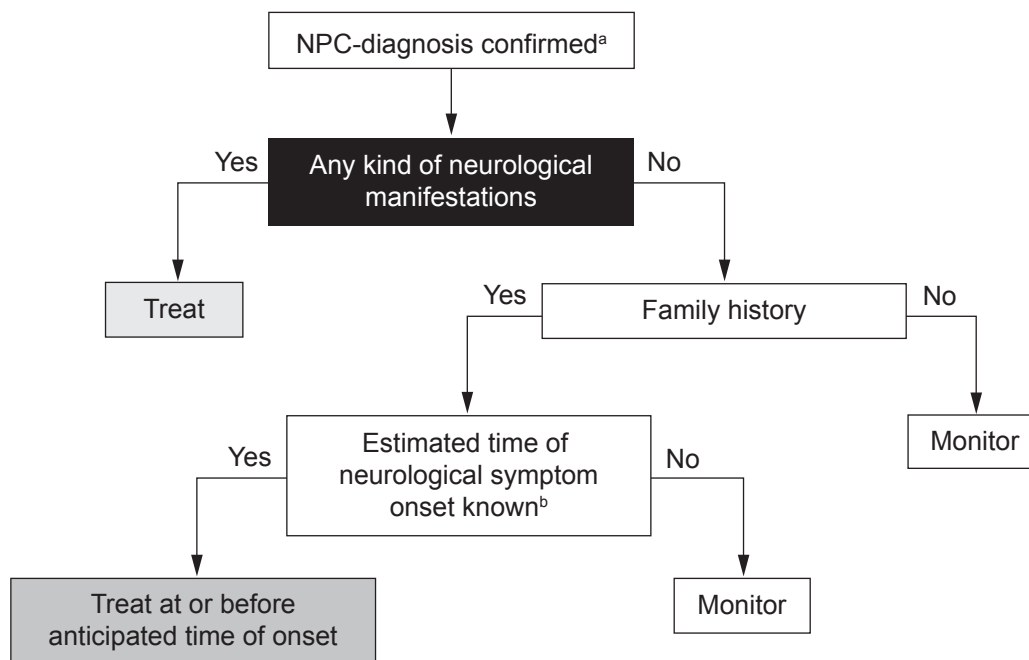


Figure 3 Protocol for initiation of miglustat treatment in NP-C. Reproduced with permission from Wraith JE, Baumgartner MR, Bembli B, et al. Recommendations on the diagnosis and management of Niemann-Pick disease type C. *Mol Genet Metab.* 2009;98:152–165.³ Copyright © 2009 Elsevier.

Notes: ^aBiochemical and/or molecular-genetic diagnosis, with or without systemic or other clinical signs and symptoms; ^bPatients asymptomatic or with isolated splenomegaly, and with one or more older siblings in whom the time of neurological symptom onset and rate of progression are known.

Table 1 Recommended miglustat dose alteration according to body surface area³

Body surface area (m ²)	Recommended dose
>1.25	200 mg three times a day
>0.88–1.25	200 mg twice a day
>0.73–0.88	100 mg three times a day
>0.47–0.73	100 mg twice a day
≤0.47	100 mg once a day

mild or moderate in intensity. Although six juvenile or adult patients and five pediatric patients experienced serious adverse events during the full 24-month study period, none of these events were considered related to miglustat therapy. Withdrawals due to adverse events occurred in four adult or juvenile patients and two pediatric patients. Mild reductions in platelet counts that were not associated with bleeding were observed in some patients. Continued monitoring of platelet counts is recommended in patients who show a reduction that is not associated with bleeding.⁴⁷

When miglustat was first launched in Europe for the treatment of GD1, a post-authorization surveillance program was established. Patients with NP-C treated with miglustat in clinical practice are also included in the database.⁶⁰ In March 2009, data had been collected from 102 patients with NP-C across 11 European countries. Miglustat was well-tolerated, with a safety and tolerability profile matching that seen in the clinical trials. Over 60% of patients had received more than 24 months' miglustat therapy, and 38% had received 36 months' treatment, demonstrating the long-term safety of miglustat in patients with NP-C.⁶⁰

There is some evidence to suggest that miglustat may have an effect on fertility. In animal studies, administration of miglustat to male mice resulted in reversible infertility in some inbred mouse strains.⁶¹ In the same study normal male fertility was reported in the rabbit. A pilot study of the effects of miglustat on spermatogenesis in healthy human men did not detect any effect on sperm motility, morphology or concentration during 6 weeks of miglustat therapy.^{61,62} However, further data are required to confirm these findings; in the meantime it is recommended that male patients should cease miglustat therapy before seeking to conceive, and maintain reliable contraceptive methods. Miglustat may also have an effect on fertility in women; for this reason miglustat should not be used during pregnancy or by breast-feeding women.⁴⁷

Patient and carer perspective

The prospective clinical trial of miglustat in NP-C did not include any quality of life or patient satisfaction and

acceptability measures, so case reports are the main source of data on the patient and caregiver perspective. Miglustat has been shown to have a positive impact upon social behavior, depression and affective and attention problems in a Brazilian patient with NP-C,⁵⁶ potentially leading to improved quality of life, not only for the patient but also for the patient's family and carers. This was reflected in the case study of two Taiwanese patients, in which families of both patients expressed satisfaction with miglustat treatment.⁵⁵ One of the patients also indicated satisfaction with treatment; the second patient was not able to express his comments despite improvements in communication during therapy.⁵⁵ In our own clinic, we have a number of patients who have achieved disease stabilization on miglustat to the satisfaction of both the patients and their parents.

Conclusions

The efficacy, safety and tolerability of miglustat in juvenile, adult and pediatric patients with NP-C have been demonstrated in a prospective clinical trial and a retrospective observational study,^{43,51–53} supported by findings from preclinical studies,^{44,48,50} case reports^{41,55,56} and the miglustat post-authorization surveillance program.⁶⁰ Miglustat may stabilize the progression of neurological manifestations in NP-C, a significant achievement in this disease, for which there has previously been no disease-modifying therapy available. Experts agree that stabilization of neurological disease is the best attainable therapeutic goal in patients diagnosed with NP-C, due to the fact that irreversible damage or loss of neurons will likely already have occurred by the time the diagnosis of NP-C is made.³ To date, miglustat is the only approved, disease-specific therapy for the treatment of NP-C. With the extension of miglustat's indication to include the treatment of progressive neurological disease in adult and pediatric patients with NP-C, treatment can now be aimed at stabilizing neurological disease progression. This represents a significant step forward in the management and treatment of this severely debilitating disorder.

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Table 2 Treatment-emergent adverse events^a in pediatric⁵¹ and adult/juvenile patients (unpublished data Wraith et al 2009) with long-term miglustat therapy (up to 52 and 66 months, respectively)

Adverse event	Pediatric (N = 12)		Adult/juvenile (N = 28)	
	n	%	n	%
Diarrhea	8	66.7	25	89.3
Tremor	7	58.3	16	57.1
Headache	6	50.0	11	39.3
Cough	5	41.7	7	25.0
Fatigue	5	41.7	13	46.4
Gait disturbance	5	41.7	–	–
Vomiting	5	41.7	9	32.1
Ataxia	4	33.3	–	–
Dysphagia	4	33.3	7	25.0
Dystonia	4	33.3	7	25.0
Flatulence	4	33.3	18	64.3
Gaze palsy	4	33.3	–	–
Nasopharyngitis	4	33.3	12	42.9
Splenomegaly	4	33.3	–	–
Cataplexy	3	25.0	–	–
Constipation	3	25.0	–	–
Deafness	3	25.0	–	–
Dementia	3	25.0	–	–
Dysarthria	3	25.0	–	–
Epistaxis	3	25.0	–	–
Fall	3	25.0	7	25.0
Hyperreflexia	3	25.0	–	–
Lethargy	3	25.0	–	–
Pyramidal tract syndrome	3	25.0	–	–
Respiratory tract infection	3	25.0	–	–
Sinusitis	3	25.0	–	–
Weight decrease	3	25.0	21	75.0
Upper abdominal pain	–	–	11	39.3
Insomnia	–	–	9	32.1
Nausea	–	–	9	32.1
Confusional state	–	–	8	28.6
Abnormal NCV ^b	–	–	8	28.6
Abdominal pain	–	–	7	25.0
Paresthesia	–	–	7	25.0
Sleep disorder	–	–	7	25.0

Notes: ^aOccurring in $\geq 25\%$ of patients, overall; ^bNCV = nerve conduction velocity.

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