Miglustat: substrate reduction therapy for glycosphingolipid storage disorders

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Miglustat (*N*-butyldeoxynojirimycin) is a potent inhibitor of ceramide-specific glucosyltransferase, the enzyme that catalyses the first committed step in glycosphingolipid biosynthesis. Inhibition of glycosphingolipid synthesis is a potential strategy for the treatment of a number of lysosomal storage disorders that result in the accumulation of glycosphingolipids within cells, an approach which has been termed substrate-reduction therapy. This article discusses the studies that led to the licensing of miglustat as a treatment for Type 1 Gaucher disease and its current and potential use in this, and other, glycosphingolipid storage disorders.

The lysosomal storage disorders (LSDs) are a family of individually rare genetic diseases characterized by the accumulation of undegraded macromolecules within the endosomal–lysosomal system of the cell [1]. LSDs are commonly classified according to which metabolites are stored within the cell (the sphingolipidoses and mucopolysaccharidoses and glycogen storage disorders). The glycosphingolipid (GSL) storage disorders are a subgroup of the sphingolipidoses that are characterized by the accumulation of glycosylated derivatives of ceramide.

These diseases are caused by deficiencies in the activity of lysosomal hydrolases, soluble enzymes which are targeted to the lysosome, in most cases via mannose-6-phosphate receptor (M6PR)-mediated uptake [2]. As well as assuring the delivery of endogenously synthesized enzyme to the lysosome, the M6PR pathway is also involved in the transfer of lysosomal hydrolases between cells, as demonstrated by the observation that storage in fibroblasts from LSD patients can be corrected by coculture with unaffected cells. This secretion reuptake pathway has been exploited in the development of enzyme replacement therapy (ERT) for a number of these diseases [3].

Licensed products are available for ERT in Gaucher and Fabry disease (and recombinant proteins are licensed or in development for the treatment of a number of other LSDs [3]). In Gaucher disease, ERT has been highly effective in reversing the organomegaly and pancytopenia seen in Type 1 disease, but has not had a significant impact on the CNS manifestations observed in Type 2 and 3 Gaucher patients [3]. The inability of circulating enzymes to cross the blood–brain barrier limits the use of ERT to conditions where there is no involvement of the brain. For LSDs where neurodegeneration is the prominent feature, alternative treatment strategies are required.

The concept of reducing substrate levels as a means of treating storage disorders (now termed substrate reduction therapy [SRT]) was first proposed by Norman Radin [4]. The aim of this novel approach is to restore homeostasis by reducing the rate of synthesis of the stored macromolecules to a level where the residual degradative activity is sufficient to prevent storage. SRT for the GSL LSDs became a real possibility with the demonstration by Platt and Butters that the imino sugar *N*-butyldeoxynojirimycin (*N*-B-DNJ, miglustat, Zavesca®) is a potent inhibitor of the ceramide-specific glucosyltransferase which catalyses the first committed step in GSL biosynthesis [5].

The use of miglustat in the treatment of the glycosphingolipidoses is discussed in this review.

Overview of the market

Gaucher disease is the most common of the glycosphingolipidoses. In the Ashkenazi Jewish population, the frequency of disease-causing alleles of the glucocerebrosidase gene is approximately 3% [6]. The predicted incidence of disease in this population would therefore be one in 850. The observed incidence of Gaucher disease in the Jewish population is, however, one in 3400, indicating that only 25% of patients with two 'Gaucher' alleles actually develop the disease. Most of these asymptomatic individuals will be homozygous for the N370S allele, which occurs at a particularly high frequency in this population [7]. Gaucher disease is much less frequent in the non-Jewish population and, for example, prevalence in the Australian population is approximately one1 in 57,000 [8].

Keywords: Gaucher disease, glycosphingolipid, lysosomal storage disorders, miglustat, substrate reduction therapy

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ERT, initially in the form of the placental-derived preparation alglucerase and, more recently, the recombinant protein imiglucerase, was licensed for the treatment of Gaucher disease in 1991. It has proven to be a highly effective treatment that has had a remarkable effect on the morbidity of Type 1 disease [3], and Genzyme estimate that over 3500 patients have so far been treated. As mentioned above, however, ERT has not been effective in treating neuronopathic Gaucher disease and it has little impact on some of the features of established bone disease (although it seems likely that early treatment might attenuate or prevent the onset of bony involvement). Furthermore, treatment with ERT involves intravenous infusion of enzyme on a weekly or fortnightly basis, which is not acceptable to all patients and not easy to deliver in all healthcare systems.

Fabry disease is an X-linked disorder due to disabling mutations in the α-galactosidase A gene. The incidence in males is approximately one in 40,000, and there is increasing evidence that hemizygote females are also affected [9]. Agalsidase-β, and agalsidase-α (TKT 4S) in Europe, were licensed for the treatment of Fabry disease in 2003. ERT for Fabry disease is thus only in its infancy and, although early experience is promising [10,11], it is far from clear whether it will be as successful as ERT for Gaucher disease.

GM1 and 2 gangliosidosis are rare neurodegenerative diseases with a combined incidence of less than one in 100,000. No disease-specific treatments have previously been available for these devastating disorders.

Neuronal ganglioside storage also occurs in other LSDs, which do not directly affect the degradative pathway for GSLs. Interestingly, conditions where there is significant storage of gangliosides share a characteristic neuropathology, termed neuraxonal dystrophy, which consists of the formation of axonal spheroids, meganeurites and ectopic dendritogenesis [12]. As well as GM1 and 2 gangliosidosis, these histologic features occur in Niemann–Pick disease types A and C, a number of the mucopolysaccharidoses and α-mannosidosis. If ganglioside storage is driving the neuropathology of these other conditions then they too may respond, at least in part, to inhibition of GSL synthesis.

A major attraction of the SRT approach is that an inhibitor of GSL synthesis could potentially be used to treat all of these disorders. To date, the only licensed inhibitor of the ceramide-specific glucosyltransferase is miglustat but a number of other compounds which inhibit this enzyme have been described, some of which are also imino sugars [13,14] and others of which are derivatives of D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP) [15]. These or similar compounds could potentially be developed in the future.

Introduction to the Compound

Imino sugars are naturally occurring polyhydroxylated alkaloids.

Chemistry

Miglustat (*N*-butyl-1,5-dideoxy-1-5-imino-D-glucitol) is an *N*-alkylated imino sugar and is most accurately described as (2*R*,3*R*,4*R*,5*S*)-1-butyl-2-(hydroxymethyl)piperidine-3,4,5-triol (**Figure 1**).

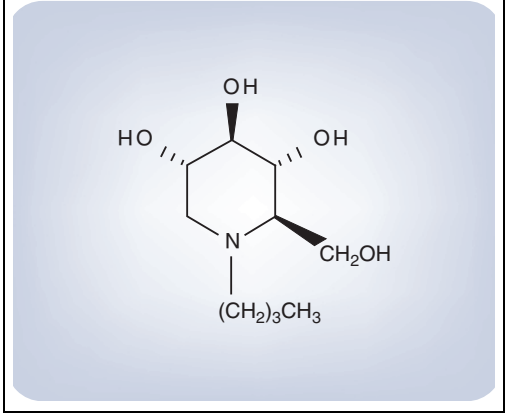
Pharmacodynamics

Miglustat is an inhibitor of a number of different enzymes. Miglustat was initially developed as an antiviral agent; its activity against endoplasmic reticulum (ER) resident α-glucosidases results in misfolding of viral glycoproteins [16]. A Phase I/II clinical trial was conducted in patients infected with HIV [17] but the agent showed no antiviral activity *in vivo* because of poor bioavailability in the ER lumen.

In vitro, miglustat is a much weaker competitive inhibitor of ceramide-specific glucosyltransferase than of the α-glucosidases, however, since this enzyme is exposed to the cytosol and is much more accessible to the drug, *in vivo* miglustat is a potent inhibitor of GSL synthesis.

Miglustat's potential as a therapeutic agent in GSL storage diseases was first demonstrated using a tissue culture model of Gaucher disease [5]. At concentrations of between 5 and 50 μM, miglustat was able to reverse glucosylceramide storage.

Figure 1. Miglustat.



Studies in normal mice demonstrated that it was possible to obtain significant reductions in the GSL content of tissues and that this was tolerated well by adult animals [18]. Animals fed 2400 mg/kg/day had miglustat serum concentrations of 56.8 µM and demonstrated a 70% reduction in GSL levels in a variety of peripheral tissues.

In the absence of a viable animal model of Gaucher disease, the concept of SRT for GSL storage disorders was tested in knockout mouse models of GM2 gangliosidosis. In a *hexA* knockout mouse (a model of human Tay Sachs disease), oral dosing with 4800 mg/kg/day produced serum miglustat concentrations in the region of 50 µM and predicted CSF concentrations of 5 µM, which was sufficient to prevent GM2 storage in the brain [19]. In the more severely affected *hexB* knockout mouse (a model of human Sandhoff disease), which not only stores gangliosides but also suffers progressive neurodegeneration, which results in death by the age of 4 to 5 months, similar dosing with miglustat from weaning resulted not only in reductions in ganglioside storage but also in significantly delayed symptom onset and a 40% increase in life expectancy [20].

Miglustat has also been given to Niemann-Pick disease type C (NP-C) mice. There is significant ganglioside storage in the brains of these animals and, histologically, they develop neuraxonal dystrophy [21]. In NP-C mice treated with miglustat, there was reduced ganglioside accumulation which was accompanied by delayed symptom onset and an increased lifespan [22]. These results confirmed the hypothesis that inhibition of GSL synthesis may be therapeutic in LSDs where there is secondary accumulation of gangliosides as well as in the primary glycosphingolipidoses.

The major toxic effects of feeding miglustat to normal mice were a 15% reduction in weight compared with litter-mate controls and a reversible atrophy of lymphoid organs, which had no demonstrable effects on immune function [18]. Diarrhea, which is thought to be due to inhibition of intestinal disaccharidases, was only seen in mice in which miglustat was administered by oral gavage; toxicology studies in rats and dogs have shown severe gastrointestinal toxicity [101]. Studies in mice have also demonstrated reversible male infertility [23]. Cataracts have been reported after chronic treatment of rats (safety data submitted to the European Agency for the Evaluation of Medicinal Products [EMEA]).

Pharmacokinetics & metabolism

Systemic bioavailability of miglustat has been measured as 82% in rats and 64% in rhesus monkeys. In humans the maximum plasma concentration is reached 2.5 h after an oral dose and the half-life is 6 to 7 h. It takes 4 to 6 weeks of treatment to reach steady-state levels [24].

After a single oral dose, levels of miglustat in the brain of multiple animal species reach about 10% of plasma levels. In steady-state dosing of normal mice, miglustat levels in the CNS are about 20% of those in plasma. In Sandhoff mice, however, penetration of the brain is higher, perhaps reflecting the CNS inflammation, which is known to be prominent in these animals [14,25]. The only published data on CNS levels in humans comes from a single patient with NP-C; levels of miglustat in the CSF were approximately 20% of plasma levels [26]. Abstracts presented at a number of meetings suggest that a similar distribution has been observed in patients with Type 3 Gaucher disease and that penetration into the brain may be somewhat greater in late-onset Tay Sachs patients.

Miglustat is not significantly metabolized and is excreted by the kidneys. Although there is active secretion of miglustat in mice, in humans, the compound appears to be cleared solely by glomerular filtration. This explains why a similar dose of miglustat gives much higher plasma concentrations in humans than in mice. These data are mostly from unpublished studies but are reviewed in the EMEA's scientific discussion of miglustat.

Clinical efficacy

As miglustat was approved under orphan drug legislation, clinical trial data are limited. The licensing application was centered on the results of a single Phase I/II study in 28 adult patients with Type 1 Gaucher disease [24]. This was an open-label, noncomparative study and involved patients unwilling or unable to take imiglucerase ERT. Patients were initially treated with miglustat 100 mg three-times daily and, in the 15 patients who stayed on this dose, this resulted in peak plasma levels of approximately 1.5 µg/ml (7.5 µM) and trough plasma levels of around 0.8 µg/ml (4 µM). In four patients the dose was reduced to 100 mg once or twice daily, either in order to maintain plasma levels in the range of 1 to 2 µg/ml (5–10 µM) or due to adverse effects and, in three patients, the dose was increased to 200 mg three-times daily in order to maximize plasma levels within the target range.

GSL depletion was demonstrated by the measurement of leukocyte cell surface GM1 levels in a subset of five patients. Over the 12-month period, mean levels fell by 38.5%. Efficacy was assessed by serial measurement of organ volumes and haematological and biochemical parameters. In the 22 patients who completed 12 months of treatment, there were significant reductions in hepatomegaly and splenomegaly (12 and 19% respectively). Improvements in haematological parameters were less dramatic with platelet count rising by a mean of 8.3×10^9/l and hemoglobin (Hb) by a mean of 0.26 g/dl. Levels of plasma chitotriosidase, a marker of Gaucher disease activity which has proven extremely useful in monitoring responses to ERT [27], had fallen by 16.4% by month 12, indicating that SRT was resulting in a reduction in the burden of storage within macrophages.

In this original study, 18 of the patients entered an extension protocol and efficacy data have now been published for 14 patients who have undergone 36 months of treatment with miglustat [28]. There were further improvements in organomegaly, with liver volume reduced by 14.46% and spleen volume by 26.4% from baseline. Hb levels in the eight patients who were anaemic at baseline (Hb < 11.5 g/dl) had increased by a clinically significant 1.28 g/dl on average. Platelet counts had risen by 20×10^9/l from baseline. Chitotriosidase levels continued to fall throughout the study.

In a subset of two patients, it was possible to assess the response to treatment of the bone marrow by using Dixon quantitative chemical shift imaging, a magnetic resonance imaging (MRI)-based technique, which allows the differentiation between normal bone marrow and marrow which is infiltrated by Gaucher cells [29]. This showed a gradual normalization of the bone marrow signal, suggesting a progressive loss of Gaucher cells.

A further study examined the effects of a lower dose of miglustat [30]. A total of 18 patients were treated with miglustat 50 mg three-times daily for 6 months. After this period, there were small, but significant, reductions in liver and spleen volumes (5.9 and 4.5%, respectively) but no improvements in hematological parameters. Thus treatment with miglustat would appear to show a dose–response effect, although whether this relates directly to the degree of substrate reduction is unclear as no data on GSL levels are available for this study.

These clinical studies formed the basis for the approval of miglustat for the treatment of patients with mild-to-moderate Type 1 Gaucher disease who are 'unsuitable' for ERT. Miglustat is not licensed for use in any of the other neurovisceral storage disorders, although Phase I/II clinical trials which might form the basis of a further application for regulatory approval are currently underway in a number of other glycosphingolipidoses (late-onset Tay Sachs disease, Type 3 Gaucher disease and Niemann–Pick disease type C) and are expected to be reported within the next 2 years.

Nonetheless, physicians have been treating individual patients with some of these conditions and as of April 2005, approximately a third of active prescriptions for miglustat were for unlicensed indications. To date, only one report of SRT in a single patient with NP-C has appeared in the literature [26]. This demonstrated that treatment with miglustat can correct lysosomal storage and cell biological features of the disease in peripheral blood lymphocytes.

Postmarketing surveillance

Actelion have established a web-based postmarketing surveillance system, which should provide data on safety and efficacy.

Safety & tolerability

The safety data submitted to the EMEA included 80 patients with Type 1 Gaucher disease who had been enrolled into various clinical trials (not all of which have been published) and an additional 240 individuals (most of whom were HIV-positive) who had been involved in other studies, many dating back to the original development of miglustat as an antiviral agent and involving doses up to ten times that initially used in Gaucher disease.

In all these studies, diarrhea was the most prominent adverse effect. Diarrhea is often seen as a first-dose effect, or following an increase in dose, and is thought to relate to inhibition of intestinal disaccharidases, which may subsequently be upregulated leading to the improvement in symptoms, although occasional episodes of loose stool are reported by many patients during chronic administration of the drug. In the original trial in Type 1 Gaucher disease, 79% of patients reported diarrhea and this led to the withdrawal of two patients from the study [24]. By month 36, however, only 36% of patients complained of diarrhea and this was predominantly of mild severity [28].

Weight loss is another frequent adverse effect of treatment with miglustat. In Type 1 Gaucher patients treated for 36 months, there was a mean weight loss of 6–7% after 12 months of treatment but, by 24 months this had disappeared.

Neurological adverse events have also been reported. 23 of the 80 Type 1 Gaucher patients treated reported tremor at some time during treatment, as did 11 of 16 Fabry patients (safety data submitted to the EMEA). Fine tremor was for the most part mild and transient, although it did lead to the withdrawal of three of the Fabry patients from the study. This seems to be a reversible toxic effect and resolves on reducing the dose or withdrawing the drug.

Paraesthesiae have also been consistently reported by about 10% of patients taking miglustat. Although these are mild and intermittent in the majority of cases, two patients have been reported who developed electrophysiologically proven peripheral neuropathy [24]. It would, therefore, seem prudent to monitor patients carefully for any symptoms or signs of neuropathy and to have a low threshold for neurophysiological testing.

Conclusion

As a theoretical concept, substrate-reduction therapy could be applied to a wide variety of inborn errors of metabolism which involve degradative pathways. The identification of miglustat as an inhibitor of the ceramide-specific glucosyl transferase provided the opportunity to test this concept in GSL storage disorders. Although these orphan diseases are rare, the experience with ERT for Gaucher disease and Fabry disease has shown that they can be viable targets for drug development. One of the advantages of the SRT approach over ERT is that inhibition of a single synthetic pathway can be used to treat a variety of storage disorders. The fact that miglustat is a small molecule with good bioavailability after oral dosing offers other advantages over the intravenous delivery of recombinant enzymes. Its ability to cross the blood–brain barrier and reach therapeutic concentrations within the brain means that miglustat may provide a therapeutic option for the diseases in which neuronal storage is not accessible to systemically delivered enzyme.

Gaucher disease was an attractive target for the development of miglustat for SRT – it is the most commont of the GSL LSDs; a treatment is already available and protocols for monitoring response to therapy are well developed; in many countries, patients attend specialist treatment centers which simplifies recruitment to and running of clinical trials. Regulatory approval was almost exclusively based on efficacy data from a single trial of miglustat in 28 adult patients with mild-to-moderate Type 1 Gaucher disease [24,28]. This trial demonstrated that treatment with miglustat results in a significant and prolonged response as measured by reductions in visceromegaly, improvements in haematologic parameters and the gradual normalization of various surrogate markers of disease activity.

Miglustat appears to be well tolerated. Although some gastrointestinal side effects are almost universal, they are generally mild, transient and easily controlled. The neurological side effects are potentially of more concern and will require careful postmarketing surveillance. It also needs to be born in mind that regulatory approval was based on safety data from only 320 patients, who had been treated with the drug for relatively short periods of time. As patients will need treatment for a lifetime, it is entirely possible that significant adverse effects have yet to manifest themselves.

Taken together, these data show that miglustat is an effective long-term treatment for Type 1 Gaucher disease. In fact, many of the patients in the extension phase of the original study were treated with doses less than the starting dose of 100 mg three-times daily for significant periods [28]; it is therefore possible that the improvements observed after 36 months would have been even more pronounced if the original, and currently recommended, dosing regime had been followed.

In both Europe and the USA the licensed indications for miglustat restrict it to use in patients where imiglucerase is not a therapeutic option. Miglustat is therefore very much a second-line agent, but deciding which patients are not suitable for ERT is not entirely straightforward. The European Working Group on Gaucher disease have published a position statement which gives guidance as to how they see the role of miglustat in the management of Type 1 Gaucher disease [31].

Expert commentary

The major obstacle to the use of miglustat in Type 1 Gaucher disease is that a highly effective and remarkably safe treatment is already available. There can no longer be any doubt that miglustat is an efficacious treatment for Type 1 Gaucher disease but there is considerable controversy concerning the relative efficacies of miglustat and imiglucerase, although no direct comparisons of SRT and ERT have been performed. The patients who have been treated with miglustat to date have suffered from relatively mild disease, but a crude analysis of data from the seminal trial of miglustat with that from similar trials of ERT suggests that, when

the severity of initial disease is taken into account, the responses obtained as measured by reductions in organomegaly were similar for both treatments whilst ERT performed slightly better for haematological parameters [32]. Nonetheless, the general consensus of opinion is that the effects of miglustat are less potent and slower in onset than those of imiglucerase, as would be expected given their different mechanisms of action. A direct comparison of SRT and ERT in more severely affected patients would be fascinating but, given the licensing restrictions, it seems unlikely that it will be carried out.

ERT is an extremely expensive treatment and is only generally available in the most highly developed countries. Increasingly, the practice in Type 1 Gaucher disease is to use high-dose, high-frequency treatment to induce remission and then gradually reduce the doses of enzyme to the minimum needed to maintain remission. Theoretically, the effects of SRT and ERT should be complementary and perhaps even synergistic, and trials of combination therapy might lead to useful advances in both initial and maintenance therapy. As well as increased efficacy, such trials might also allow reductions in the dose and/or frequency of enzyme infusions, which would be welcome to patients although, given the high cost of miglustat, might not contribute significantly to cost control.

Despite the fact that the vast majority of patients manage their regular infusions very well, they would prefer an effective and safe oral treatment. This is the major potential advantage that miglustat has over imiglucerase. Therefore, although its use will initially be limited, it is possible that patient demand will eventually be the major driving force towards the more general use of SRT in Type 1 Gaucher disease.

Highlights

- Substrate reduction therapy is a potential approach to a variety of storage disorders
- Miglustat is an inhibitor of ceramide-specific glucosyltransferase and can potentially be used for substrate-reduction therapy in disorders in which there is primary or secondary glycosphingolipid storage.
- Miglustat has bee licensed as a second-line treatment for Type 1 Gaucher disease
- Unike recombinant enzyme, miglustat can enter the brain and has been shown to be effective in animal models of neurovisceral storage disorders.
- Clinical trials are currently underway in patients with Type 3 Gaucher, late-onset Tacy-Sachs and Newmann-Pick type C disease. Miglustat may prove to be the first effective therapy for these, and other, related, diseases.

In this authors view, the major potential of SRT is in the treatment of other glycosphingolipidoses, particularly those which involve the brain and for which ERT would not be an option. The effects of miglustat in mouse models of Sandhoff disease and NP-C have been truly remarkable. These mice make no functional protein, and the best that could be hoped is that SRT would delay the inevitable accumulation of GSL within cells. In contrast, in all but the most severe forms of human disease, there is a degree of residual protein activity and it is therefore possible that treatment with miglustat could decrease GSL synthesis to a level which would allow normal homeostasis to be restored, preventing further storage and giving the opportunity for the gradual clearance of the accumulated glycolipid.

Although clinical trials are underway in a number of these conditions and significant numbers of patients are being treated 'off-label', at present no clinical efficacy data are available. It is by no means certain that the current studies will provide definitive answers: these are slowly progressive disorders with highly variable features and many patients will need to be treated for long periods; we do not know which of the patients' functional defects result from irreversible neuronal loss and which (if any) from dysfunction due to potentially reversible storage; no one has yet described reproducible ways to measure clinical progression or response in these conditions. All the data available indicate that miglustat should help these patients, but it will require an ongoing commitment from clinicians and funding bodies to realise this potential.

Outlook

In 5-years time we should know a lot more about the adverse effects of miglustat therapy. If no new safety concerns arise, then there is likely to be a growing demand from patients for oral treatment for Type 1 Gaucher disease.

Some patients with neurovisceral GSL storage disorders, particularly NP-C, Tay Sachs disease and Sandhoff disease, will have been treated for a number of years. It will become clear that these patients do get real clinical benefit from SRT and there will be pressure to license miglustat for these indications so that treatment can be commenced as early as possible in the course of the disease.

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