NTSAD Web Page on Miglustat

Fran Platt

Substrate Reduction Therapy for LSDs

Background

Several lysosomal storage diseases (LSDs) involve the storage of fatty molecules within cells of the body that are called sphingolipids (*1*). This is because an enzyme that normally works to break these molecules down in the lysosome, the waste disposal/recycling center of our cells, does not work properly (*2, 3*).

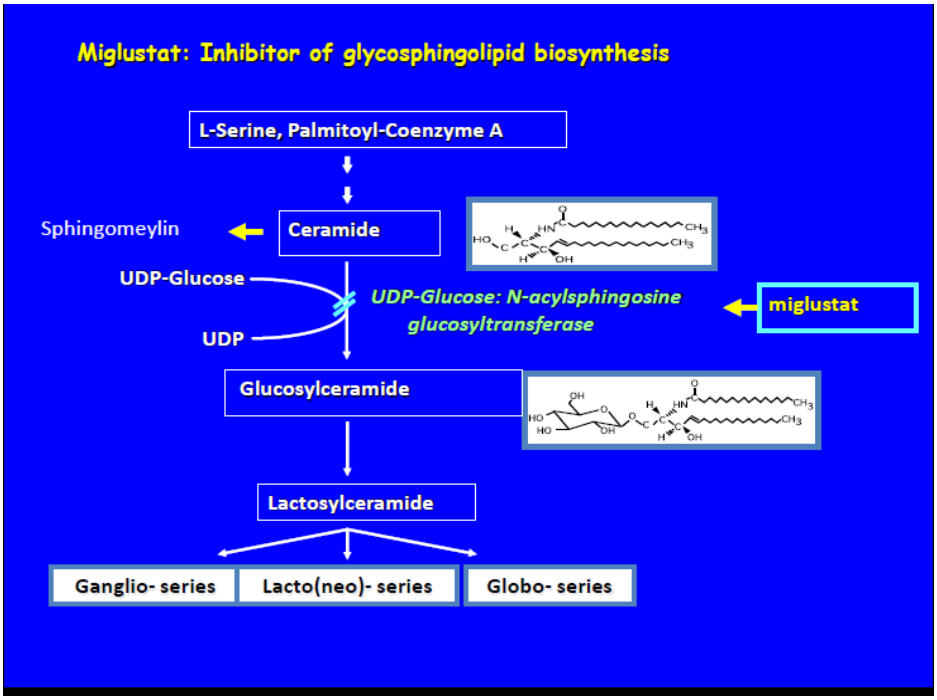
Some sphingolipids are modified by the cells of our bodies by adding sugars, creating a family of specialized sphingolipids called glycosphingolipids (GSLs) (*1*).

For example, in Gaucher disease a glycosphingolipid called glucosylceramide is not broken down and is stored, whereas in Tay-Sachs and Sandhoff disease it is a glycosphingolipid called GM2 ganglioside that is stored (*1*).

Glycosphingolipids are made in the cells of our bodies by a single metabolic pathway that begins with the addition of a sugar molecule called glucose to a sphingolipid molecule called ceramide (*1*). The fact that there is only a single major pathway to make most glycosphingolipids offers a potential way of treating these diseases using a small molecule drug (*4*).

How would a drug work?

The principle behind this treatment is called **substrate reduction therapy (SRT)**(*4*). The idea is to partially block the cells in our body from making glycosphingolipids, specifically stopping them from adding glucose to ceramide, which is the first step in this pathway. This would mean fewer glycosphingolipids are made, so fewer would require breaking down in the lysosome. The aim is to balance the rates of glycosphingolipid manufacture with their impaired rate of breakdown.



What is the SRT drug?

The first drug approved by the FDA in the United States and the EMA in Europe as a substrate reduction therapy was miglustat (*5*). Miglustat is a small molecule drug that looks like a sugar molecule and was first developed by the American company Monsanto in the 1980s as an anti-viral drug for treating HIV, based on a known enzyme target (*6, 7*).

A clinical trial in HIV patients was conducted, and although it did not help treat HIV, it did produce a large body of safety data for this drug in animals and in humans. This meant it could potentially be repurposed fairly rapidly for treating other diseases.

Fran Platt and colleagues at the University of Oxford (UK) found that this drug had another very surprising activity, that it prevented the first step in glycosphingolipid formation (*8*). She and her colleagues worked for many years to use this drug (working with Oxford GlycoSciences initially and then with Actelion Pharmaceuticals who now market the drug under the brand name Zavesca) to treat LSDs (*9*).

Miglustat is a drug that can be taken by mouth as a tablet and gets into the blood stream and into the brain (*5*). The drug was tested in several mouse models of LSDs and showed a reduction in storage levels in the brain and extended the life span of the mice; for example in a mouse model of Tay-Sachs disease (miglustat reduced storage)(*10*), Sandhoff (miglustat reduced storage and increased the life span of the mouse)(*11*) and GM1 gangliosidosis (miglustat reduced storage and improved function)(*12*).

Clinical Trial in type 1 Gaucher disease

Based on these findings, miglustat was evaluated in patients with type1 Gaucher disease and the drug was demonstrated to be effective. (*13, 14*). Miglustat was then marketed as an alternative treatment for Gaucher disease, offering an oral alternative to patients unable or unwilling to receive intravenous enzyme replacement therapy (*15*).

SRT in Niemann-Pick type C (NPC) Disease

Glycosphingolipids are also stored in diseases that are not due to lysosomal enzyme deficiencies, including NPC disease (*16*). Walkley and colleagues speculated that the storage of GSLs (such as GM2 ganglioside), may also contribute to pathology in NPC disease (*17*). Therefore, they treated the mouse model of NPC disease with miglustat and it delayed onset of clinical neurological disease and extended life span (*17*). Subsequent studies in cats with NPC disease also showed significant clinical benefit (*18*). The precise mechanism of action of miglustat in NPC disease remains incompletely understood. The drug was then evaluated in clinical trials in patients with NPC and was found to be effective in slowing disease progression. Miglustat is now approved virtually worldwide for treatment of NPC disease, except by the FDA for use in the United States (*19-21*). However, since the FDA approves it for other uses, it is prescribed off-label by many U.S. physicians for individuals with NPC disease.

Side effects of miglustat

Miglustat is a small molecule drug that resembles glucose (*22*). Within our bodies there are several enzymes that are involved in glucose metabolism and this drug inhibits some of these enzymes, leading to some side effects.

The main side effect of miglustat is inhibition of enzymes in the gut that function to digest complex carbohydrates (*23*). As a result, complex carbohydrates from the diet that are normally absorbed from the small intestine end up undigested. They enter the large intestine where they draw water into the bowel (due to osmotic effects of these carbohydrates), leading to diarrhea(*24*). This is often of mild to moderate severity and easily managed with a medication called loperamide. The diarrhea typically resolves after a month or so of treatment (*5*). Some dietary modifications can reduce the impact of this side effect by minimizing complex carbohydrates in the diet (*25*).

Weight loss also occurs in patients treated with this drug and this is likely due to the appetite suppressant activities of miglustat that have been demonstrated in mice (*26*).

In some patients with type 1 Gaucher disease in the original clinical trial, miglustat worsened peripheral neuropathy (symptoms often include tingling and burning in the hands and feet (*13*), but this has not been seen in patients with

NPC. Tremor (shakiness) was also a side effect in the Gaucher studies and was managed by reducing the drug dose (*5*).

New Generation of SRT Drugs

Very recently (August 2014), Genzyme developed a new SRT drug, approved by the FDA, for treating patients with type 1 Gaucher disease. Eliglustat inhibits the same key enzyme in glycosphingolipid biosynthesis that is targeted by miglustat. Eliglustat is more specific than miglustat and does not inhibit the gut enzymes miglustat inhibits, and so does not cause diarrhea. It showed clinical benefit in a number of clinical trials (*27-41*). Its side effects differ from miglustat and include urinary tract infection, headache and peripheral pain as the most common side effects. The drug was generally well tolerated and the side effects were of mild to moderate severity (*27*).

Eliglustat is not a suitable SRT drug for treating LSDs that affect the brain as unlike miglustat it does not cross the blood-brain barrier.

Potential role of miglustat in GM1 and GM2 gangliosidoses.

In view of the effectiveness of miglustat reported in NPC disease (*19*) (another neurodegenerative disease) and its subsequent approval by the drug regulators, would miglustat also be useful for treating the ganglioside storage diseases (e.g. Tay-Sachs, Sandhoff and GM1 gangliosidoses)?

Animal models have shown that treating mice with Tay-Sachs, Sandhoff, and GM1 with miglustat before symptoms of disease arise is helpful (*10, 11, 42*).

However, a clinical trial of miglustat did not demonstrate benefit in patients with late onset Tay-Sachs disease (*43*). It remains unclear whether earlier treatment in more mildly affected patients would result in benefit. It will be important to collect more information about patients before starting future trials, so that the effects of the medication can be measured better.

There are reports of benefits to individual patients with Tay-Sachs disease treated with miglustat (*44, 45*). Miglustat is not an effective treatment for patients with infantile-onset (disease symptoms beginning before 1 year of age) as these children have too little residual enzyme to break down the remaining gangliosides that are made. However, further studies in patients with later onset diseases are warranted if coupled with detailed natural history studies to allow better interpretation of the outcomes of the trial.

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