GUIDELINES FOR TREATMENT OF GAUCHER DISEASE WITH MIGLUSTAT (v.2)

Preamble

Gaucher disease is a rare hereditary condition caused by deficiency of the enzyme, glucocerebrosidase, which is required for the breakdown of a specialized lipid, called glucocerebroside which occurs throughout the body but particularly in the liver, spleen, and bone marrow. Accumulation of glucocerebroside in people with Gaucher disease often causes no problems at all. The only problem in many is enlargement of the spleen which may cause alterations in the blood leading to easy bruising or a tendency towards prolonged bleeding following injuries, minor surgery, or the birth of a baby. The bleeding tendency is caused by depletion of blood platelets and is correctable in part by surgical removal of the spleen. However, splenectomy accelerates the accumulation of the lipid in the liver and bone marrow.

Individuals with Gaucher disease often are chronically anemic as a result of replacement of normal bone marrow by "storage cells". Although anemia is common, it is rarely severe. However, in some cases the anemia progresses to a stage requiring regular and frequent blood transfusions; rarely, it leads to death.

In some individuals with the disease, accumulation of glucocerebroside in the bone marrow causes weakening of the bone causing fractures. In a few, disturbances of the circulation to the bone cause periodic attacks of excruciating pain in the hips, knees, and shoulders. In these individuals, interruption of the circulation to the bone often causes destruction of joints resulting in a requirement for major surgical treatment. People with Gaucher disease are also more apt than others to develop bone infections. Accumulation of glucocerebroside in the liver may cause cirrhosis, resulting in bleeding into the stomach and gut, jaundice, swelling of the ankles, and, eventually, death.

Treatment of Gaucher disease in the past has focussed on symptomatic treatment of pain; surgical treatment of fractures, infections, and avascular necrosis of bone; surgical removal of the spleen to relieve the thrombocytopenia caused by hypersplenism; and blood transfusions to correct the anemia of the disease. Patients with very severe disease have also been treated by bone marrow transplantation. However, this requires the availability of a suitable bone marrow donor, and the procedure is associated with prolonged hospitalization and morbidity and with a high mortality rate.

Treatment of Gaucher disease by enzyme replacement therapy represents a major advance in the treatment of genetic disease. The enzyme that is deficient, glucocerebrosidase, has been extracted from human placenta and chemically modified to enhance its effectiveness. Treatment with this modified product has dramatic effects on the hematologic and bone complications of the disease - on this issue the results of all the reported clinical trials are unambiguous. The efficacy of enzyme replacement in the management of other complications is still under investigation.
Experience has shown that some patients with type I Gaucher disease (non-neuronopathic Gaucher disease) do not tolerate enzyme replacement therapy, or cannot qualify for medical, religious, or personal reasons. The introduction of a new treatment, which aims to decrease the production of glucocerebroside, rather than accelerating its elimination, represents a potential therapeutic option for patients in this category.

Substrate reduction therapy with miglustat decreases the production of glucocerebroside by inhibiting glucosylceramide synthase (UDP-glucose:ceramide glucosyltransferase). The drug has been shown, in clinical trials, to produce improvements in the enlargement of the liver and spleen and the anemia and decreased platelet counts in patients with type I Gaucher disease. It has also been shown to stabilize therapeutic gains achieved by enzyme replacement therapy. The drug is administered orally, which for some, represents a major advantage over intravenous enzyme infusion. However, treatment with miglustat is associated with side effects which limit its use, and it has not been evaluated in the treatment of neuronopathic Gaucher disease or in children with type I Gaucher disease.

What follows are some guidelines for the use of miglustat in the treatment of Gaucher disease, developed initially by a group of physicians involved in the management of patients with the disease who met in Ottawa on May 26, 2005. The guidelines were then circulated among a larger group of Canadian physicians for suggestions for modifications. The final result is a consensus statement, based to a considerable extent on the guidelines developed by the Advisory Council to the European Working Group on Gaucher Disease, published in the Journal of Inherited Metabolic Disease, vol. 26, pp 513-526, 2003, modified to take into consideration the Canadian context.

**Guidelines**

**General comments**

1. The treatment of choice for moderately severe or severe Gaucher disease is enzyme replacement therapy (ERT).

2. Substrate reduction therapy with miglustat does provide an effective alternative to enzyme replacement therapy in adults who are unsuitable candidates for ERT.

3. Treatment with miglustat should be considered only in patients who would otherwise be considered candidates for ERT, but are unable for various reasons to submit to it.

4. Treatment with miglustat is associated with some unpleasant and potentially serious side-effects, which must be taken carefully into consideration in deciding upon using it in individual patients. Patients must be made fully aware of these side-effects, and must be followed closely by appropriate studies for the early detection and treatment of known, suspected, or potential adverse reactions to the drug.

5. The safety and efficacy of miglustat therapy for patients with severe Gaucher disease has not been established. However, it may have a role to play, along with ERT, in the
treatment of patients with severe disease who are incompletely responsive to ERT alone.

6. The safety and efficacy of miglustat therapy for patients with neuronopathic Gaucher disease (types II and III) has not been demonstrated.

7. The safety and efficacy of miglustat therapy in children and adolescents has not been demonstrated.

Recommendations

1. Substrate reduction therapy with miglustat should be considered in patients with moderate type I Gaucher disease who are unable or unwilling to receive enzyme replacement therapy, including:
   a. Patients unwilling or unable to receive ERT for medical or personal reasons
   b. Patients who are unsuitable for ERT
   c. Patients who are incompletely responsive to maximum doses of ERT

2. Miglustat should only be prescribed for adults by experts, based in dedicated centres, who are familiar with the treatment of Gaucher disease.

3. The decision to use miglustat, rather than ERT, at any stage of disease activity, should be based on clinical criteria alone and not related to issues of potential cost.

4. The potential adverse effects of miglustat requiring safety monitoring, compared with ERT, should be discussed with the patient before the drug is prescribed.

5. Treatment with miglustat in patients with neuronopathic Gaucher disease should only be undertaken in the context of a formal clinical trial.

6. The use of miglustat in children or adolescents with Gaucher disease is not recommended at this time.

Dosage

1. The dosage of miglustat recommended by the advisory group is 100 mg three times daily, the dosage shown in clinical trials to be effective in the treatment of type I Gaucher disease. The use of lower dosages, which have also been studied in clinical trials, is not recommended.

Monitoring of therapy

1. Patients on treatment with miglustat should be assessed before the initiation of treatment and at least every 6 months thereafter for:
a. Effectiveness of treatment, using the guidelines developed and periodically modified by the International Collaborative Gaucher Group (see *Seminars in Hematology*, vol 41(Suppl 5), pp 15-22, 2004)

b. Adverse reactions, by neurological examination (including mental state assessment), nerve conduction studies, plasma folate and vitamin B_{12} levels, and whatever other studies the treating physician deems to be indicated in individual cases.

**Adjunctive therapy**

1. The occurrence of adverse gastrointestinal reactions to treatment with miglustat is decreased by treatment with a lactose-free diet, supplemented by oral administration of lactase and, in some patients, by treatment with loperamide.

**Further studies**

The group recognized the pressing need for further formal studies to examine the role of SRT in the treatment of patients:

- with type I Gaucher disease who have had a good response and are stable on ERT.
- with mild type I Gaucher disease.
- with type III Gaucher disease.

**Bibliography**


Pastores GM, Rolfs A, Miranda MC, Zimran A; Advisory Council to the European Working Group on Gaucher Disease. The role of the iminosugar N-butyldeoxy-


