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Miglustat

A Viewpoint by Ernest Beutler

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The concept that inhibiting the formation of glucocerebroside might be useful in the treatment of Gaucher's disease is not new. This approach was espoused by N. Radin and others in the 1970s and 1980s, but concern that blocking the synthesis of a vital component of cell membranes might prove very toxic prevented clinical trials. It was only when *N*-butyl deoxynojirimycin (miglustat) was investigated as a treatment for AIDS that it became clear that even relatively large doses of this inhibitor could be tolerated without excessive toxicity. However, by this time, enzyme replacement therapy (ERT) was available and has become the standard against which new treatments must be measured.

The use of miglustat in the treatment of Gaucher's disease has some distinct potential advantages over ERT. The drug is relatively cheap to manufacture. It can be given orally, a distinct advantage over the weekly intravenous infusions of enzyme needed for near-maximum effect. In addition, ERT has not been clearly effective in the treatment of neuronopathic disease, and the penetration of a small molecule inhibitor such as miglustat might provide more effective management of the neuronopathic manifestations of type 2 and 3 Gaucher's disease.

However, miglustat has some distinct disadvantages when it is compared with enzyme replacement. The inhibitor seems to be somewhat less efficacious than enzyme replacement, particularly with respect to correction of haematological abnormalities. More importantly, there are some disturbing toxicities. The very same drug has been proposed as a treatment for AIDS, as a male contraceptive, as a treatment for Tay-Sachs disease, as an antiviral agent, and as a treatment for Fabry's disease. It is not surprising that an agent that interferes with this many processes might have a considerable number of adverse effects. The diarrhoea that it causes is apparently easily controlled and may disappear on its own accord, but the neurological symptoms, neuropathy or tremor, are of greater concern, although they appear to be reversible. The fact that neurons are not replaced leads to concern regarding the potential for long-term neurological effects.

Miglustat is approved for use in patients who cannot or will not take ERT. Based on lower efficacy and higher toxicity than ERT, this seems entirely appropriate. What seems most important about this new therapy is that it can serve as a starting point for the synthesis of more specific inhibitors that presumably have fewer adverse effects and possibly higher effectiveness. ▲