Institution: University of Oxford

Unit of Assessment: UOA5

Title of case study:

Miglustat: the first oral treatment for rare but devastating lysosomal storage disorders

1. Summary of the impact

Professor Platt and colleagues at the University of Oxford have developed the drug miglustat, the first oral therapy for rare lysosomal storage diseases. These are primarily neurodegenerative diseases that affect 1 in 5,000 live births, always leading to premature death. In 2009, miglustat became the first treatment to be licensed for treating neurological manifestations in Niemann-Pick disease type C (NPC). It is now prescribed for the majority of NPC patients worldwide, and has led to significant improvements in both life expectancy and quality of life. Miglustat was approved for type 1 Gaucher disease in 2002 and, since 2008, has proved an effective treatment for patients previously stabilised with enzyme replacement therapy; miglustat has the additional benefit of improving bone disease. Sales of miglustat since 2008 have generated CHF 315 million in revenues for Actelion, the company sublicensed to sell the drug.

2. Underpinning research

Lysosomal storage disorders (LSDs) are a family of over 60 rare but devastating human disorders caused by the malfunctioning of lysosomes in cells. When lysosomes fail to function correctly, excess products destined for breakdown and recycling (especially glycosphingolipids) are stored in the cell and can accumulate to pathological levels. In most LSDs, the central nervous system is severely affected. Individually, LSDs occur with incidences of less than 1 in 100,000; however, as a group, the incidence is about 1 in 5,000 live births. Tens of thousands of people are affected worldwide, with many dying within a few months or years of birth. Others die of these diseases following years of suffering from various symptoms of their particular disorder. For many affected patients, no specific therapy is available apart from symptomatic management and palliative care.

The first breakthrough in a potential treatment for LSDs occurred serendipitously in 1994. Professor Platt (then at Oxford University's Department of Biochemistry; now at the Department of Pharmacology) had been working on a glucose analogue drug called *N*-butyldeoxynojirimycin (*N*B-DNJ, now miglustat), determining how it disrupted the life cycle of HIV. During electron microscopy analysis of a human cell line treated with *N*B-DNJ, Platt observed an apparent thickening of the plasma membrane in treated cells. With hindsight, this was probably the result of the stain detecting the presence of *N*B-DNJ, but this observation took the research in a new direction. This led Platt (in collaboration with Terry Butters at the Oxford Glycobiology Institute and with Monsanto) to carry out experiments exploring what, if any, changes in membrane lipid composition occurred in the presence of *N*B-DNJ. It was found that phospholipid composition was unaltered in *N*B-DNJ treated cells, but glycosphingolipids (GSLs) were absent. The interpretation of this unanticipated finding was that *N*B-DNJ was inhibiting GSL biosynthesis and could therefore offer a means of regulating GSL levels in cells[1]. It was immediately clear that *N*B-DNJ could potentially provide an oral-based treatment for LSDs, in which pathological accumulation of GSLs is a major factor. Platt termed this approach 'substrate reduction therapy' (SRT).

The next step was to determine the degree to which GSLs could be depleted *in vivo* in a mammalian species. Platt and colleagues orally treated normal mice with *N*B-DNJ over several months and achieved 70% depletion of peripheral GSLs without causing any overt toxicity. This paved the way for evaluation of *N*B-DNJ-mediated SRT in mouse disease models. For these studies Dr Rick Proia (US National Institute of Health) generated knock-out mouse models of two LSDs, Tay-Sachs disease and Sandhoff disease, leading to the first experimental demonstration that *N*B-DNJ can cross the blood-brain barrier and reduce GSL storage in the brain[2].

This landmark study led to the evaluation of the drug in an acute neurodegenerative mouse model

of Sandhoff disease. Treatment with *N*B-DNJ was found to delay disease progression, reduce neuro-inflammation, improve neuromuscular function, and prolong life expectancy[3]. Concurrently with this research, clinical collaborators and a commercial partner (Oxford Glycosciences, a company spun out from the University of Oxford's Department of Biochemistry) tested *N*B-DNJ in patients with type 1 (non-neuronopathic) Gaucher disease in an international one-year open-label clinical trial. The trial demonstrated significant reductions in the size of the liver and spleen, and improved haematological abnormalities[4]. The drug was named miglustat and approved in Europe for use in type 1 Gaucher disease in 2002, and in the USA and Israel in 2003. Since then Actelion has marketed it under the brand name Zavesca.

Platt and colleagues then turned their attention to another LSD: Niemann-Pick disease type C (NPC), previously considered to be a cholesterol storage disorder. They demonstrated that treating a patient with miglustat reduced pathological lipid storage, improved endosomal uptake and normalised lipid trafficking. Since miglustat has no direct effect on cholesterol metabolism, this research indicated that accumulation of GSLs was in fact the primary pathogenic event in NPC, and, therefore, that miglustat could be an effective treatment for patients with NPC[5]. An international clinical trial followed, and in 2009 miglustat was approved by the European Medicines Agency for treating NPC.

Platt has also demonstrated the potential for miglustat to slow or arrest the course of disease in other LSDs with central nervous system pathology (for example, Tay-Sachs disease and Sandhoff disease), as the drug is able to cross the blood-brain barrier. In addition Platt's group have developed a second-generation compound for SRT, the galactose analogue *N*B-DGJ. This compound is devoid of side effects and shows greater tolerability at high dose, and it is now in phase I trials for potential clinical development[6].

3. References to the research

1. Platt FM, Neises GR, Dwek RA, Butters TD. (1994) *N*-butyldeoxynojirimycin is a novel inhibitor of glycolipid biosynthesis. Journal of Biological Chemistry 269: 8362–8365. Available from: http://intl.jbc.org/content/269/11/8362.full.pdf ***First publication demonstrating that miglustat inhibits glycosphingolipid biosynthesis, the biochemical basis for its clinical mechanism of action.***

2. Platt FM, Neises GR, Reinkensmeier G, Townsend MJ, Perry VH, Proia RL, Winchester B, Dwek RA, Butters TD. (1997) Prevention of lysosomal storage in Tay-Sachs mice treated with *N*-butyldeoxynojirimycin. Science 276: 428–431. doi: 10.1126/science.276.5311.428 ***First publication showing that miglustat reduces lysosomal storage in the brain of an animal disease model.***

3. Jeyakumar M, Butters TD, Cortina-Borja M, Hunnam V, Proia RL, Perry VH, Dwek RA, Platt FM. (1999) Delayed symptom onset and increased life expectancy in Sandhoff disease mice treated with *N*-butyldeoxynojirimycin. Proc Natl Acad Sci USA 96: 6388–6393. doi: 10.1073/pnas.96.11.6388 ***First publication showing that miglustat increases life expectancy and neurological function in an animal disease model.***

4. Cox T, Lachmann R, Hollak C, Aerts J, van Weely S, Hrebícek M, Platt F, Butters T, Dwek R, Moyses C, Gow I, Elstein D, Zimran A. (2000) Novel oral treatment of Gaucher's disease with *N*-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. Lancet 355: 1481–1485. doi: 10.1016/S0140-6736(00)02161-9 ***Pivotal clinical trial of miglustat in patients with type 1 Gaucher disease, leading to European Medicines Agency (EMA) and US Food and Drug Administration (FDA) approval.***

5. Lachmann RH, te Vruchte D, Lloyd-Evans E, Reinkensmeier G, Sillence DJ, Fernandez-Guillen L, Dwek RA, Butters TD, Cox TM, Platt FM. (2004) Treatment with miglustat reverses the lipid-trafficking defect in Niemann–Pick disease type C. Neurobiol Dis. 16: 654–658. doi: 10.1016/j.nbd.2004.05.002 ***First study to demonstrate cellular correction by miglustat in a patient with NPC disease.***

6. Andersson U, Smith D, Jeyakumar M, Butters TD, Borja MC, Dwek RA, Platt FM. (2004) Improved outcome of *N*-butyldeoxygalactonojirimycin-mediated substrate reduction therapy in a mouse model of Sandhoff disease. Neurobiology of Disease 16: 506–515. doi: 10.1016/j.nbd.2004.04.012 ***First* in vivo *study showing increased benefit of a second-generation miglustat analogue (NB-DGJ), paving the way for future development of a drug with a minimal side-effect profile.***

Funding for research: Grants in the region of £3.9M were awarded between 1996 and 2009 from The Wellcome Trust, MRC, Action Medical Research UK and The Ara Parseghian Medical Research Foundation.

4. Details of the impact

The development of miglustat has had a profound effect on the lives of people suffering from two LSDs: Niemann-Pick disease type C (NPC) and type 1 Gaucher disease.

First licensed by the European Medicines Authority (EMA) for NPC in January 2009, miglustat is the first therapy to be approved for patients with the condition. This disease usually affects children of school age, but onset can occur at any time from early infancy to adulthood. Previously there were no treatments to relieve the multiple and severe symptoms, which include difficulty with upward and downward eye movements, difficulty with swallowing, ataxia, dystonia, learning difficulties with progressive intellectual decline, tremors accompanying movement and, in some cases, seizures. In infants, NPC can also compromise liver function.

In most countries, all NPC patients who meet treatment guidelines are now prescribed miglustat; the exception is the USA, where the figure is nearer 50% as the drug is still awaiting FDA approval. While not curing NPC, miglustat substantially slows disease progression. The drug has a large volume of distribution and the capacity to access deep organs such as the brain, bones, and lungs, making it particularly effective in managing the central nervous system aspects of NPC[7]. There is evidence that, if used early enough, miglustat may even prevent the development of neurological symptoms[8]. A systematic review from 2012 examined how miglustat improved swallowing difficulties in NPC patients, suggesting that this also reduced patients' risk of developing bronchopneumonia (a common cause of death in NPC) and resulted in greater life expectancy compared to untreated patients[9]. The chair of the US National Niemann-Pick Disease Foundation, arguing for the drug to be licensed for NPC in the US, stated that treatment with miglustat slows the 'relentless progression' of the disease and gives months or years of improved quality of life[10].

Miglustat has been licensed since 2002 for some patients with type 1 Gaucher disease. This is the most common of the LSDs, caused by an enzyme deficiency which leads to a collection of fatty material in the spleen, liver, kidneys, lungs, brain, and bone marrow. Symptoms include an enlarged spleen, anaemia, fatigue and bruising. Severe and disabling bone pain and fractures are also common; untreated patients typically become dependent on wheelchairs owing to this. The disease is primarily treated using intravenous enzyme replacement therapy, but miglustat provides a highly important and effective oral alternative for patients for whom enzyme therapy is unsuitable or becomes unsustainable owing to damage caused by repeat injections.

Since 2008, however, miglustat has shown itself to have two other significant applications in the treatment of type 1 Gaucher disease. Firstly, it is an effective oral therapy for the long-term maintenance of patients previously stabilised with enzyme replacement therapy[11]. Secondly, there is evidence that miglustat reduces the incidence of bone pain and improves bone mineral density in type 1 Gaucher disease, even more effectively than enzyme replacement therapy[12]. In 2008 this led to the EMA approving a type II variation for Zavesca (miglustat), so that guidance on the positive effect of miglustat on bone disease in type 1 Gaucher disease was included in the medicine's information sheet[13].

Sales of miglustat have shown a dramatic rise from CHF 6.1 million in 2004 to CHF 84.7 million in 2012. Since 2008, sales have more than doubled, totalling CHF 315 million, and they continue to

rise; in the first quarter of 2013 sales were 23% up on the same quarter in 2012[14]. Given the limited market for this drug in patients with two very rare diseases, this continuing sales growth is notable, especially since for one of those diseases, type 1 Gaucher, miglustat is only licensed for the treatment of patients for whom enzyme replacement therapy is unsuitable. To date the drug has been used to treat several hundred patients with type 1 Gaucher disease and NPC worldwide.

5. Sources to corroborate the impact (indicative maximum of 10 references)

7. Pineda M et al. (2009) Miglustat in patients with Niemann-Pick disease type C (NP-C): a multicentre observational retrospective cohort study. Mol Genet Metab. 98: 243–249. doi: 10.1016/j.ymgme.2009.07.003 ***Paper independently reporting clinically relevant beneficial effects of miglustat on neurological disease progression in patients with NPC.***

8. Di Rocco M et al. (2012) Early miglustat therapy in infantile Niemann-Pick disease type C. Pediatr Neurol. 47: 40–43. doi: 10.1016/j.pediatrneurol.2012.04.005 ***Study indicating that miglustat may be more effective in preventing neurological symptoms, the earlier it is used.***

9. Walterfang M et al. (2012) Dysphagia as a risk factor for mortality in Niemann-Pick disease type C: Systematic literature review and evidence from studies with miglustat. Orphanet Journal of Rare Diseases 7: 76 doi: 10.1186/1750-1172-7-76 ***Independent review examining the increase in life expectancy associated with NPC patients taking miglustat, as a result of improvements in swallowing.***

10. Chickering Wilson P. FDA reviews potential Niemann–Pick drug. Daily Union. http://www.nnpdf.org/documents/DailyUnionarticlereZavescaFDAReview.pdf ***US newspaper report from 2010 on testimonials to the FDA from the National Niemann-Pick Disease Foundation and from US families affected by Niemann-Pick disease type C.***

11. Giraldo P et al. (2009) Real-world clinical experience with long-term miglustat maintenance therapy in type 1 Gaucher disease: the ZAGAL project. Haematologica 94: 1771–1775. doi: 10.3324/haematol.2009.008078 ***Independent study reporting that miglustat is an effective therapy for the long-term maintenance of patients with type 1 Gaucher disease who have previously stabilised with enzyme replacement therapy.***

12. Pastores GM, Elstein D, Hrebícek M, Zimran A. (2007) Effect of miglustat on bone disease in adults with type 1 Gaucher disease: a pooled analysis of three multinational, open-label studies. Clin Ther. 29: 1645–1654. doi: 10.1016/j.clinthera.2007.08.006 ***Report based on three independent studies suggesting that miglustat can have a positive influence on bone disease in type 1 Gaucher disease.***

13. European Medicines Agency (EMA) document on changes to Zavesca since authorisation. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000435/WC500046725.pdf ***Variation relating to miglustat and bone disease in type 1 Gaucher disease is detailed on p5.***

14. Actelion Pharmaceuticals Ltd. Annual report archive. Switzerland: Actelion Ltd; 2013 Apr 29. Available from: http://www1.actelion.com/en/our-company/annual-report/annual-report-archive.page ***Archive of Actelion's annual reports detailing Zavesca sales.***