Chapter 2
Alternative Treatment Options: Enzyme Replacement and Small Molecule Therapies

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2.1 Enzyme Replacement Therapy

Initial attempts at enzyme replacement therapy (ERT) for lysosomal storage disease (LSD) began in the 1970s using enzyme extracted from placenta or urine. Although some proof of concept was obtained, it quickly became apparent that there were a number of problems that needed solution before this approach could be developed further into a useful therapy for affected patients [11].

These initial problems included an inability to produce pharmacological quantities of enzyme necessary to treat all patients, an inability to target the infused enzyme to all tissues and a lack of animal models on which to evaluate this new approach to therapy. Consequently interest in this approach to treatment declined and other forms of therapy were pursued culminating in the introduction of bone marrow transplantation in the early 1980s. The identification of the mannose-6-phosphate receptor in the late 1970s was a pivotal moment for subsequent development of ERT but one that could not be exploited at that time [25].

A breakthrough of importance in ERT was made in the early 1990s when it was demonstrated that 2–3 mg/kg of placental derived, mannose-terminated, β-Glucosidase markedly improved haematological indices and reduced hepatosplenomegaly in patients with type I Gaucher disease [3, 4]. The demonstration that fortnightly infused enzyme was well tolerated, apparently free from side-effects and efficacious in reversing many years of substrate accumulation, confirmed that this clinical approach to treatment for non-neurological LSDs was worthy of pursuit.

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Genzyme, a (then) small biotechnology company founded in June 1981, purified and modified β-glucosidase from human placenta collected on an industrial scale. The resulting enzyme, marketed as Ceredase, revolutionized the treatment and outcome for many sufferers of this progressive disorder. Advances in gene identification and cloning led to the subsequent production of and demonstration of equal efficacy of recombinant human enzyme (produced in Chinese hamster ovary (CHO) cells. The introduction of Cerezyme® [16] led to the withdrawal of the placental product. As a parallel development, the identification and availability of animal models (especially domestic species, e.g. MPS I dog and MPS VI cat) allowed for the first time new therapies to be studied carefully in a preclinical setting.

Currently available therapies include three ERTs for Gaucher disease (Imiglucerase, Genzyme; Velglucerase alfa, Shire Human Genetic Therapies and Taliglucerase alfa, Protalix) two products for Fabry disease (Agalsidase alfa, Shire Human Genetic Therapies and Agalsidase beta, Genzyme) as well as products for MPS I (Laronidase, BioMarin), MPS II (Elaprase, Shire Human Genetic Therapies), MPS VI (Galsulfase, Biomarin), Pompe disease (Aglucosidase alfa, Genzyme). A treatment for MPS IV A is in clinical trial and recombinant enzymes for deficiencies of sphingomyelinase, arylsulfatase A and alpha-mannosidase are in the pipeline.

2.1.1 Goals of Treatment

Before considering individual disorders it is important to have a clear idea of what one hopes to achieve from therapy. In LSDs these aims can be summarized as follows. The treatment should be safe and the level of storage within the cells or organs of the individual should be reduced and as a consequence the natural history of the disease should be altered favourably. Effective treatment should leave a minimal residual disease burden and the burden of treatment should be less than the burden of the illness. Finally, the treatment should be affordable [61].

2.1.2 The Expected Response to Treatment

It would be hoped that if ERT or any other therapy were to be instituted before symptoms the patient would remain asymptomatic. For treatment commencing after the patient has begun to show clinical signs it would again be hoped that the patient could be returned to an asymptomatic state. In reality for most LSDs there is a residual disease burden as with time most disorders are associated with irreversible damage. The size of the residual disease burden is critical in assessing the success or failure of an individual therapy. To give an example, some patients with infantile Pompe disease will continue to exhibit marked skeletal muscle dysfunction despite dramatic improvement in cardiomyopathy following ERT. If the skeletal muscle disease is severe enough to require full-time ventilation because of respiratory

muscle weakness, the residual disease burden is enormous and many would doubt the efficacy of the underlying therapy, especially as it has to be maintained regularly at great expense.

The end result of a variable residual disease burden in a group of heterogeneous disorders is the production of multiple, different, new clinical phenotypes whose natural history is unknown.

2.1.3 Individual Disorders Treated by ERT

2.1.3.1 Gaucher Disease

Gaucher disease (GD) is an autosomal recessive disorder resulting from a deficiency of β-Glucocerebrosidase (β-Glucosidase, GBA, EC 3.2.1.45). The enzyme deficiency results in an accumulation of glucosylceramide (GlcCer, glucosylcerebroside) primarily within cells of the macrophage–monocyte system leading to the characteristic "Gaucher cell". The disorder is particularly common in individuals of Ashkenazi Jewish origin [62] and has an estimated worldwide prevalence of around 1:75,000 births [17].

The disorder produces a clinical spectrum of disease that has for convenience been traditionally described as three types depending on the presence or absence of neurological involvement:

- Type I non-neuronopathic
- Type II acute neuronopathic
- Type III chronic neuronopathic

There is no evidence that ERT can influence favourably the neurological components of GD II or III. It can however improve the visceral disease seen in GD III and ERT should be prescribed for these patients. Some groups also favour the use of ERT in GD II as part of a package of palliative care aimed at improving symptoms but this approach has not been met with uniform approval. The majority of patients on treatment will however have type I disease and it is in this group that the major benefits of therapy are seen.

Early treatment with Cerzyme® (Imiglucerase, Genzyme) in GD I results in an improvement in anaemia, thrombocytopenia, organomegaly, bone pain and bone crises. Treatment regimens have varied but most are now based on the recommended licensed dosage of 60 Units/kg/2 weeks. Many patients show significant improvements on a lower dose and a compelling case can be made for a more individualized approach to dosage regimens [20]. Therapeutic goals have been established against which therapy can be monitored [37] and long term safety of ERT has been assessed from patient registry data [50].

The success of Cerezyme® therapy in the treatment of GD I has encouraged the development of two further enzyme products. The first product Velglucerase alfa (Shire Human Genetic Therapies) is made by gene activation in a human cell and as

a consequence is believed to be more favourably glycosylated resulting in increased cellular uptake when compared to Cerezyme® [7]. The third product, Taliglucerase alfa (Uplyso®, Protalix) is produced in a plant based expression system. Velaglucerase (Vpriv) has now been licensed for use [63]. The worldwide shortage of imiglucerase (Cerezyme®) beginning in late 2009 highlighted the need for alternative products to be available even for very rare disorders [22].

2.1.3.2 Fabry Disease

Fabry disease is an X-linked disorder caused by deficiency of the lysosomal enzyme α-Galactosidase A (GLA, EC3.2.1.22). The resulting accumulation of globotriaosylceramide leads to a wide spectrum of clinical signs and symptoms that affect many organs, including the brain, heart and kidney [8]. Unlike most other X-linked disorders carrier females often exhibit signs and symptoms of organ damage similar to affected males [56]. The incidence of Fabry disease has been estimated to be 1 in 40,000 to 1 in 117,000 worldwide although data from newborn screening programmes suggests that late onset variants may be much more common than this [49].

HSCT has never been suggested as a potential therapy for Fabry disease. Although untreated patients die much younger than average the mainstays of treatment until the introduction of ERT were palliative therapies including medications to control pain, renal replacement therapy and cardiac medications [31].

Outside of the USA both agalsidase alfa (Replagal®, Shire Human Genetic Therapies) 0.2 mg/kg every other week and algasidase beta (Fabrazyme®, Genzyme) 1 mg/kg every other week are available as ERT to treat Fabry disease, whereas in the USA only agalsidase beta has been approved so far.

Clinical trials have suggested efficacy of both products and the evidence supporting this has recently been reviewed [46]. In brief, the timely introduction of ERT can prevent disease progression in many patients with Fabry disease, but in some patients with advanced disease ERT may slow down but not prevent end organ failure [2].

2.1.3.3 Pompe Disease

Glycogen storage disease type II (GSD II, Pompe disease) is an autosomal recessive disorder caused by a deficiency of acid alpha-Glucosidase (GAA, EC 3.2.1.20). The classic infantile form of the disease (Pompe disease) is associated with muscular hypotonia and a rapidly progressive hypertrophic cardiomyopathy that leads to death in the first year of life in the majority of affected patients [27]. Late onset forms (juvenile or adult onset GSD II, also known as acid maltase deficiency) are primarily a disorder of skeletal muscle (often mistaken for limb girdle muscular dystrophy) leading to progressive problems with mobility and respiratory function. Cardiomyopathy is not a feature of late onset variants [59]. The history of ERT for Pompe disease, culminating in the development of Myozyme® (Alglucosidase alfa, Genzyme), has been reviewed recently [53].

Unlike other LSDs the dosage of enzyme required to effect an improvement in clinical condition is much higher in Pompe disease (20 mg/kg/dose compared with 0.2–1.0 mg/kg/dose). In addition, ERT is much more effective in clearing glycogen from cardiac as opposed to skeletal muscle. In the latter type II fibres are particularly difficult to treat [44]. Despite these limitations ERT has demonstrated long term efficacy in infantile Pompe disease [28] as well as leading to improvements in late onset variants monitored over a 12 month period [51].

2.1.3.4 Mucopolysaccharidoses

Successful clinical trials have led to the approval of ERT for MPS I, II and VI [18, 35, 60]. Modest improvements in respiratory function, growth and endurance are common after the institution of therapy but ERT cannot influence the development of CNS disease as the enzymes are unable to cross the blood–brain barrier. Attempts have been made to establish criteria or guidelines for therapy but these still generally remain nationally based and differ from country to country. A major challenge is deciding on the role of ERT in patients with significant cognitive impairment. The use of ERT in severely affected patients as part of a general package of palliative care is favoured by some groups whilst others refuse or are not allowed to prescribe for patients with significant learning disability. Whatever the degree of cognitive impairment is present it is important to have clearly defined treatment goals and be prepared to discontinue therapy in patients who appear to be gaining no benefit from treatment.

In patients with spinal cord compression due to dural hyperplasia intra-thecal ERT (as well as intravenous) may be an appropriate approach to therapy and prevent the need for invasive surgery [36]. The fact that enzyme can be delivered safely by this route also allows the consideration of using this method of treatment to try and obtain brain penetration in those disorders associated with cognitive impairment e.g. Mucopolysaccharidosis type III (San Filippo disease). This approach has already been tried in MPS III dogs and a clinical trial in human patients with MPS III is underway [19]. A clinical trial of intra-thecal idursulfase (Shire HGT) for cognitive impairment in MPS II is also underway.

The currently approved preparations with their recommended dosages are Aldurazyme® (Laronidase, Biomarin) 100 units (0.58 mg)/kg/week for MPS I, Elaprase® (Idursulfase, Shire Human Genetic Therapies) 0.5 mg/kg/week for MPS II and Naglazyme® (Galsulfase, Biomarin) 1 mg/kg/week. A Phase III clinical trial of recombinant galactosamine 6-sulfatase (GALNS, BMN 110, Biomarin) for MPS IVA (Morquio disease) has been completed and met the primary endurance related end point.

2.1.3.5 Other Disorders

ERT is in development for a number of other disorders including sphingomyelinase deficiency (Niemann–Pick disease type B, NPB, Genzyme), arylsulfatase A

deficiency (metachromatic leucodystrophy, MLD, Shire Human Genetic Therapies), alpha mannosidase deficiency (alpha mannosidosis, Zymenex), lysosomal acid lipase deficiency (Wolman disease, Synageva corp) and there are likely to be others.

2.1.4 Limitations of Enzyme Replacement Therapy

The clearly documented safety and efficacy of ERT in GD has led Cerezyme® to be regarded as the "gold standard" against which all other products are compared even though the disorders being treated are diverse. Although there is no doubting the efficacy of Cerezyme® in GD, there are clearly some limitations [12]. First, the treatment is intravenous, although it can be delivered safely in the patient's home. Second, the therapy is ineffective in neuronopathic disease even if instilled directly into the cerebrospinal fluid and has relatively poor efficacy against pre-existing bone and lung disease. Finally like all recombinant protein products, the treatment is expensive and therefore unless funded by charitable means, is unavailable to patients in countries that have more pressing health care concerns. Despite Cerezyme's clear shortcomings none of the subsequently developed ERTs approach its efficacy due to the nature of these other disorders and due to limitations of the enzyme products themselves.

2.1.4.1 Limitations of Therapy Due to the Nature of the Disease

For most of the disorders under treatment we lack a comprehensive knowledge of the natural history of the disease. This is not surprising as most clinicians, even in very big clinics, will not see the full range of presentations of these individually rare disorders. Furthermore there is increasing evidence that some of the clinical symptoms associated with LSDs may be initiated by processes secondary to the storage of substrate. It is by no means certain that ERT can "switch-off" these secondary effects, and the resulting pathogenic cascades could go on to produce further damage to tissues and organs despite timely introduction of ERT. This whole area of lysosome biology and LSD pathogenesis has been reviewed recently [54].

With the exception of Gaucher disease, where Cerezyme® has been available for a number of years, our knowledge about the efficacy of the products is based on clinical trials performed on patients with relatively advanced disease. The reasons for this are understandable—the disorders are rare, there is a need to demonstrate a clinical effect quickly and the patients that are able to cooperate with sophisticated testing are therefore older and inevitably have more advanced disease than those younger patients who would perhaps be too immature to cooperate fully with testing. Until we are able to judge the ability of the various enzymes to *prevent* disease, by being used in a prophylactic manner following early diagnosis of the LSD, we will remain unaware of the full potential of this therapy.

Finally, for most of the disorders, we lack biomarkers and severity scores to allow us to judge the stage of the disease in the individual and also the efficacy of the therapy in reducing the disease burden. The role of biomarkers in LSDs has recently been reviewed [10] and a number of severity scores have also been produced recently to try and address these deficiencies and to aid with assessing efficacy [15, 58].

2.1.4.2 Limitations of the Treatment Itself

Unfortunately, none of the currently prescribed ERTs is able to treat all aspects of the disorders equally. Animal studies have revealed organ-specific variations in response to ERT. Among other studies showing similar results, ERT in the dog model of MPS I, for example, produced no significant changes histologically in cartilage and heart valve despite high-dose therapy for a prolonged period [24]. Experience has shown that bone, cartilage, heart valves and brain remain especially resistant to correction by intravenous ERT, and alternative methods of delivery or targeting will be needed if these problems are to be overcome. There is some evidence that very early (presymptomatic) treatment by ERT may lead to a much better outcome [13]. However, until ERT can be linked to a newborn screening programme for LSDs, this question will remain unanswered as the majority of patients present with a significant disease burden.

Of increasing concern is the development of specific antibodies against the infused proteins. Whilst severe infusion associated reactions are fortunately rare and usually manageable [26, 34] antibodies that inhibit enzyme activity or block uptake of enzyme into the cell are of more concern. The clearest clinical example of this is seen in infantile Pompe disease where patients with mutations that lead to the production of no natural protein (CRIM negative, Cross Reactive Immunologic Material negative) have a much worse outcome than patients that are CRIM positive and this is directly related to the early onset and very high antibody titres seen in the CRIM negative patient [29]. Successful attempts at eliminating antibodies to Myozyme® in Pompe disease has been reported [32, 33] but in most patients with very high titres and deteriorating clinical disease this has proved impossible and most patients will succumb to their disease. What is becoming clear is that for a small number of patients with all the disorders under treatment with enzyme replacement therapy significant immunological reactions will limit benefit and indeed may put the patients at risk [45]. Immune tolerance regimens and better understanding of the role played by these antibodies need to be developed quickly if these patients are to benefit from this major advance in therapy [55].

The final limitation to treatment is the financial burden, which makes therapy difficult to obtain for those in countries that have more pressing health care needs. As an example the approximate cost *per year* for a 70 kg adult patient with Gaucher, Fabry and Pompe disease on licensed dosages of Cerezyme®, Fabrazyme®, Replagal® and Myozyme® is £200,000, £118,000, £130,000 and £269,000 (taken from prices in British National Formulary [bnf.org], March 2009 and using dosages

of 60 mg/kg, 1 mg/kg/, 0.2 mg/kg and 20 mg/kg respectively). For patients with a mucopolysaccharide disorder, who are generally smaller, the approximate costs for a 40 kg patient with MPS I (Aldurazyme®), II (Elaprase®) and VI (Naglazyme®) are £192,000, £310,000 and £255,000 (taken from prices in British National Formulary [bnf.org], March 2009 and using dosages of 100 units/kg/week, 0.5 mg/kg/week [rounded down to take into account vial size] and 1 mg/kg/week) respectively.

2.2 Conclusions

ERT has been a major advance in the treatment of LSDs. Many disorders now have therapy and our efforts should be aimed at improving targeting to brain and bone, where considerable limitations still remain. The full potential of ERT has not yet been realized because the majority of patients treated either in clinical trials or on commissioned therapy have had advanced disease and we will only understand the full impact of this therapy when it is used on a cohort of patients identified soon after birth.

For the majority of patients the treatment will be safe but there is increasing concern about immune reactions leading to treatment failures in a significant minority of patients with most diseases with the possible exception of Gaucher disease.

Cost remains an issue for many countries. The treatment is expensive and, as more complicated and less prevalent disorders are targeted for therapy, costs have risen, so that ERT remains impossible to obtain for many affected patients.

2.3 Substrate Reduction Therapy

Substrate reduction therapy (SRT) offers a different approach to the therapy of LSDs by reducing the rate of synthesis of macromolecules (for example glycosphingolipids, GSL) to a level where any residual enzyme activity in the cell is sufficient to prevent substrate accumulation. It should be possible over time to reverse storage and storage related pathologies. This approach has been exploited with the development of Zavesca® (Miglustat, Actelion) an *N*-alkylated imino sugar and a synthetic analogue of D-glucose. Zavesca® is an inhibitor of the enzyme glucosylceramide synthase, which is a glucosyl transferase enzyme responsible for the first step in the synthesis of most GSLs. An advantage of Zavesca® is that it is of low molecular weight as well as being active orally. It is known to cross the blood–brain barrier and therefore offers a potential therapy for LSDs with a CNS component due to an accumulation of GSLs.

The most common adverse effects of Zavesca® seen in clinical trials and confirmed in post marketing surveillance are diarrhoea (mild to moderate) and weight loss (6–7 % of body weight) occurring in 80 % and 65 % of treated patients respectively. More serious complications such as peripheral neuropathy have been reported

and Zavesca® is also contraindicated in pregnancy, but on the whole the product has been well tolerated. More details about safety and tolerability can be found on the Zavesca® website (www.zavesca.com).

2.3.1 Gaucher Disease

In Gaucher disease the primary disease pathology is associated with the storage of specific GSLs and therefore would seem the ideal disorder to respond to SRT with Zavesca®. Subsequent clinical trials indeed led to the approval of Zavesca® by both the EMEA and the FDA for use in Gaucher disease type I patients felt to be unsuitable for ERT. This would include patients with very difficult venous access, needle phobia or a history of allergic reactions to Cerezyme®. Detailed guidance on the use of Zavesca® in type I Gaucher disease has been published [57] and long term post authorisation follow up studies have confirmed a favourable safety profile [21].

Most of the therapeutic goals in Gaucher disease (including improvements in bone disease) that have been established for ERT can also be met by Zavesca® but at a slower rate. This is to be expected given the differing modes of action of Cerezyme® and Zavesca® [38].

The attractiveness of an oral therapy for Gaucher disease has led to the development of other possible substrate inhibitors. Genz-112638 is a novel glucosylceramide analogue and when given orally partially inhibits glucosylceramide synthase, resulting in reduced production of glucosylceramide. The drug is claimed to have high potency and favourable results were obtained in a Phase II study [40]. A definitive Phase III study started enrolling patients in late 2009.

2.3.2 Niemann–Pick Disease Type C

Niemann–Pick Disease type C (NPC) is an inherited neurodegenerative disorder characterized by an intracellular lipid-trafficking defect with secondary accumulation of glycosphingolipids. A clinical trial of Zavesca® in NPC showed improvement or stabilization of a number of clinically relevant markers of disease activity over a 12 month period [39]. A number of subsequent observational studies have confirmed disease stabilization (especially in patients with more slowly progressive disease) but longer studies are needed to confirm whether or not the stabilization represents a temporary or permanent state [14, 41].

A major difficulty is deciding when to start Zavesca® in NPC patients. About a third of affected patients present with liver disease in the newborn period and of these the majority go on to make a full recovery only to re-present later with neurological signs and symptoms. The pre-symptomatic period may be many years, even decades in this group of patients [23]. It would be tempting to start Zavesca® as soon as the liver disease resolves but that would mean potentially many years on therapy

in the absence of symptoms with the additional uncertainty of not knowing whether the absence of symptoms was due to the drug or the natural history of the disease in the particular individual. In addition the long term effects of inhibiting GSL production in the presence of an immature CNS are unknown.

2.3.3 Other Disorders

Unfortunately Zavesca® has not shown the same degree of efficacy in other neurodegenerative LSDs. Clinical trials in Gaucher disease type III [47], Juvenile Sandhoff disease [30], late onset Tay-Sach's disease [48] have all failed to demonstrate a disease stabilizing effect from Zavesca®.

2.3.4 Other Substrate Reduction Therapies

Genistein (4′,5,7-trihydroxyisoflavone or 5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) is the most abundant isoflavone in soy and one of its many actions is to inhibit the synthesis of glycosaminoglycans (GAGs) demonstrated in skin fibroblasts from patients with mucopolysaccharidoses [42]. Genistein has also been shown to cross the blood–brain barrier achieving levels of approximately 10 % of those attained in blood [52]. This combination of features make genistein an attractive candidate for treating mucopolysaccharidosis type III (San Filippo disease) and double blind, placebo controlled, clinical trials are anticipated in the near future.

Substrate optimization therapy (SOT) is a newly suggested approach based on making substrates more amenable to degradation by modifying their chemical structure without reducing the overall amount produced. It is claimed that this can be achieved in MPS disease by small molecules modifying the glycan sulfation pattern of the GAG biosynthetic enzymes [6].

2.3.5 Conclusions

Oral substrate reduction therapy currently has a limited role to play in the management of LSDs. There are clear indications for use of Zavesca® in type I Gaucher disease in patients unable to tolerate ERT. Other indications are less certain with the exception of Niemann–Pick disease type C where a disease stabilizing effect has been demonstrated. In animal models SRT has shown a synergistic effect with bone marrow transplantation and anti-inflammatory treatment and therefore in the future role of SRT may be as an adjunct to other modalities of treatment rather than being a primary therapy in isolation [43].

2.4 Chaperone Mediated Enzyme Enhancement

Certain DNA missense mutations lead to the production of proteins that are misfolded but which often retain active functional domains. The misfolded proteins produced in this way are usually blocked within the endoplasmic reticulum where they are degraded by the proteosomal system. Some low molecular weight ligands that are usually competitive inhibitors of these proteins can bind to the functional domains and in sub-inhibitory concentrations act as chaperones, rescuing the protein and allowing its transfer to the lysosome where the active functional domains can initiate some hydrolytic activity. The end result is a small increase in residual enzyme activity which in the individual patient may be enough to convert a severe disorder into a more attenuated form. The advantages of this approach are similar to those of SRT, namely that these chaperones are active orally and as they are of low molecular weight they can generally cross the blood–brain barrier. A major disadvantage is that this form of therapy is very mutation dependent and will not be suitable for the many patients that have disease caused by large DNA deletions or nonsense mutations associated for instance with no protein or the production of very truncated proteins.

As yet, no products of this type have fulfilled the regulatory requirements for licensing.

Amicus Therapeutics Inc. (Cranbury, NJ, USA) have led the way with this form of therapy and have a number of clinical trials in progress aimed at developing chaperone therapy for Fabry, Gaucher and Pompe disease. Although the respective products are at different stages of development the Pompe programme (AT 2220) ran into difficulties when two of the patients on the Phase II study deteriorated significantly on therapy. The FDA subsequently terminated this trial and Amicus plan to initiate a further phase I study of AT2220 specifically to gather more pharmacokinetic data and dependent on the results of this study further trials in patients may recommence (http://ir.amicustherapeutics.com/releasedetail.cfm?ReleaseID=412487).

Late onset Hexosaminidase A (Hex A) deficiency is another disorder often associated with misfolded and prematurely degraded protein. Cell culture studies subsequently revealed evidence of enzyme enhancement after exposure of the cells to the antimalarial pyrimethamine a competitive inhibitor of Hex A. An open-label Phase I/II study has recently reported encouraging preliminary results [9].

Once again combination therapies utilizing chaperones as adjuncts to more definitive therapies are likely to be the main role for this form of treatment.

2.4.1 Conclusions

Like SRT, chaperone therapy is likely to play a small role in the treatment of LSDs. The need for compliant mutations limits its use in many disorders and combinations of ERT, SRT, chaperones and cell based therapies perhaps offer the best chance of successful outcomes in disorders associated with CNS disease.

2.5 Stop Codon Read Through

In contrast to both SRT and chaperone therapy the efficacy of stop codon read through therapy depends on the presence of nonsense mutations within the gene leading to premature stop codons. A number of LSDs, especially the more severe variants, are caused in this way. PTC124® (Ataluren, PTC Therapeutics) is the first investigational product to be developed aimed at providing a mechanism for the ribosome to ignore the premature stop codon and allow some full length protein to be produced. This effect has previously been noted with aminoglycosides as well as some other compounds but the doses required in cell culture to gain an appreciable effect on residual enzyme activity are too high to be used in humans without the risk of severe side effects [5]. As yet there are no clinical trials of PTC124® in human LSDs although studies in cystic fibrosis, haemophilia and Duchenne muscular dystrophy have been initiated (http://clinicaltrials.gov/ct2/results?term=PTC+124).

2.6 Final Conclusions

ERT has made a contribution to improving the quality of life for many patients with LSDs. The positive clinical benefits are seen most keenly in Gaucher disease and whilst the other ERTs have not reached the same degree of efficacy, clinical improvements have been seen in many patients with Fabry, Pompe and mucopolysaccharide disease. Clinical efficacy depends on the stage of the disease when treatment commences (some disease elements are irreversible once established) and whether or not the patient generates neutralizing or blocking antibodies to the infused protein. Oral, small molecule therapies, have made less of an impact on patient outcome so far. There is a small, but clearly defined, place for the use of Zavesca® in Gaucher disease and Niemann–Pick disease type C, but other indications are so far lacking. Other substrate inhibitors are at a much earlier stage of development as are chaperone and other small molecule therapies. It may be that these treatments will never be stand-alone but will be destined to play a part in multi-modality therapy in combination with more definitive treatments such as transplantation or gene transfer.

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