Pharmacological Therapy in Inborn Errors of Metabolism

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Abstract

Different therapeutic principles can improve clinical outcome in patients suffering from inborn errors of metabolism (IEM). IEMs are inherited disorders which are based on a primary enzyme defect or deficiency of a cellular transporter. Substrate reduction by diet (exogenous substrate), pharmacological substrate reduction (endogenous substrate), supplementation of a missing cofactor/vitamin, activation of alternative pathways for the elimination of toxic compounds, augmentation of enzyme activity by chaperones and enzyme replacement therapy (in selected diseases like lysosomal storage diseases) are therapeutic options for alimentary and pharmacological treatment in IEM.In this chapter we will discuss options for pharmacological and/or dietary therapy in selected prototype IEM.

Introduction

Inborn errors of metabolism (IEMs) are inherited disorders which are either due to a primary enzyme defect or deficiency of a transporter. In enzyme deficiencies, the physiological substrate of the enzyme reaction accumulates, while the product of this reaction (distal to the reaction) is decreased. Accumulation of substrates can occur

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F. J. Hock, M. R. Gralinski (eds.), *Drug Discovery and Evaluation: Methods in Clinical Pharmacology*,
https://doi.org/10.1007/978-3-319-56637-5_62-1

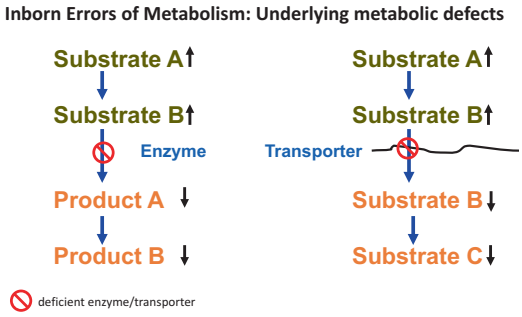

Fig. 1 Principles of inborn errors of metabolism (IEMs): IEMs are either due to an enzyme deficiency of compromised transporter function. This leads to the accumulation of the substrate of the deficient enzyme and reduced levels of its product or accumulation of the substrate of a deficient transporter in one cell compartment

quickly, especially in catabolic states or during dietary indiscretions, thus intoxicating the organism. Therefore, this group of IEM is called "intoxication-type" IEM. If an intracellular transporter is compromised, the substrate to be transported accumulates in one cell compartment and is low in others (storage disease, e.g., lysosomal storage disorders (LSD)) (Fig. 1). As it takes some time until substantial levels of substrate accumulate, these disorders mostly have a more chronic course, with the exception of M. Niemann-Pick type C where neonatal liver failure occurs in some patients.

All IEMs are rare diseases, so-called orphan diseases. In Europe, these are defined as diseases affecting fewer than 5 in 10,000 inhabitants, in the USA a disease affecting less than 200,000 inhabitants (<1:1,500), and in Japan a condition present in less than 50,000 inhabitants (<1:2,500) is called an orphan disease.

It was Sir Archibald Garrod who first described an IEM, namely, alkaptonuria, which is a disorder in the degradative pathway of the amino acid tyrosine, and coined the notion "Inborn Error of Metabolism" more than 100 years ago (Garrod 1902). Today, several hundred IEMs are known; each year new IEMs are described.

Based on the rarity of IEM, it is difficult to perform randomized controlled studies; mostly a multinational, multicenter approach is required. The development of new therapies is challenging for pharmaceutical companies as the small patient number renders the studies necessary for approval by regulatory bodies difficult; at the same time, the economical return is limited after approval is granted resulting in a high financial burden per patient for the health system. Politically, the challenges for treating patients with orphan diseases have been recognized, and measures have been taken to support pharmaceutical companies in marketing orphan drugs. For example, the European Medicines Agency (EMA) offers protocol assistance free of charge to companies intending to market orphan drugs; on the other hand, marketing exclusivity for these compounds is longer (10 years), and a reduced fee for approval is levied for orphan drugs. This has led to the approval of 128 new orphan drugs from 2000 to 2016; 1805 drugs got orphan drug designation (http://www.ema.europa.eu/ema/). Nineteen percent of orphan drugs were approved for the indication "alimentation and metabolism."

For many IEM, a good, meaningful outcome parameter is missing. Obviously, the clinical outcome can be judged; sometimes the substrate and the product of the missing enzyme can be measured (e.g., phenylalanine and tyrosine in phenylketonuria (PKU)) to monitor the therapy.

Therapeutic Principles of Treatment in IEM

Understanding the pathophysiology of an IEM is essential for designing a therapy. If the disease is due to an enzyme defect, reducing the substrate and supplementing the product of the compromised enzymatic reaction are useful. In diseases where the enzyme substrate is administered via food, dietary measures are promising. The prototype of these disorders is classical phenylketonuria (PKU) where a low-protein diet has to be followed, while tyrosine, the product of the deficient phenylalanine hydroxylase, is supplemented by a special amino acid mixture. If an endogenous substance is the substrate of the deficient enzyme reaction, pharmacological inhibition of the synthesis of the substrate is an option (substrate reduction therapy). In some

patients with an enzyme deficiency, the enzyme is not completely absent; chaperones can stabilize the enzyme resulting in an increased residual activity. Some enzymes depend on a cofactor which may be deficient due to an IEM. In these diseases, supplementation of the cofactor is helpful (e.g., in biotinidase deficiency). In other IEMs, alternative excretion pathways may be activated by pharmacological treatment leading to the excretion/elimination of accumulating toxic substances by alternative pathways (e.g., in urea cycle defects, benzoate and butyrate can eliminate nitrogen atoms independently of the compromised urea cycle). Chaperones are able to stabilize the structure of the deficient enzyme; only mutations where the enzyme is still present, hence milder mutations, are amenable to enzyme augmentation by chaperones. For a small number of IEMs, it is possible to produce the missing enzyme in a bioreactor using cell cultures, couple the enzyme to mannose 6-phosphate or expose mannose 6-phosphate, and apply the drug to the patients via intravenous infusion every week or every other week depending on the underlying disease. Via mannose 6-phosphate receptors on the cell surface, the enzyme is taken up and is trafficked to the lysosome to replace the missing enzyme. Such therapeutic options exist for some of the so-called lysosomal storage disorders.

In some disorders where the enzyme is localized exclusively or predominantly in a single organ, solid organ or cell transplantation can be offered to replace the missing enzyme. These procedures are not without risk and lead to chronic disease burden (immunosuppression, risk of infection, transplantation-associated malignancies); therefore alternative treatment options should be carefully considered. Transplantation will not be discussed further in this article which is focused on dietary and pharmacological treatment strategies.

In summary, we have the following options for alimentary and pharmacological treatment in IEM:

1. Substrate reduction by diet (exogenous substrate)
2. Pharmacological substrate reduction (endogenous substrate)
3. Supplementation of a missing cofactor/vitamin
4. Activation of alternative pathways for the elimination of toxic compounds
5. Augmentation of enzyme activity by chaperones
6. Enzyme replacement therapy (in selected diseases like lysosomal storage diseases)

Obviously, it will not be possible to discuss options of pharmacological therapy in all IEMs; examples for these therapeutic options will be presented in the following sections of this chapter. Some pharmacological compounds used for the treatment of IEM were originally developed for other purposes; during toxicity testing, it was revealed that these substances have effects on metabolic pathways. This will be exemplified in the section on pharmacological substrate reduction in patients suffering from tyrosinemia type 1.

Substrate Reduction by Diet

Classical phenylketonuria (PKU) due to phenylalanine hydroxylase (PAH) deficiency is the prototype of this group of IEM amenable to dietary treatment.

The pathophysiology of the disease was discovered in 1934 by A. Folling (Christ 2003) which was the basis for treating the condition. In PKU, the metabolism of phenylalanine is impaired due to variants of the gene encoding PAH. Usually, PAH converts phenylalanine to tyrosine requiring tetrahydrobiopterin (BH4) as cofactor. PAH deficiency leads to the accumulation of phenylalanine in the blood and brain. If left untreated, this condition will lead to irreversible brain damage presenting with intellectual disability, severe developmental delay, psychiatric abnormalities, epilepsy, and microcephaly (Blau et al. 2010).

In their seminal work, H. Bickel and coworkers in 1953 showed the positive clinical effect of a low-protein diet (without meat and fish) supplemented with an amino acid formula devoid of phenylalanine and rich in tyrosine, essential

amino acids, vitamins, and minerals (Bickel et al. 1954). Today, low-protein diet is still the cornerstone of treatment in classical PKU; new age-adjusted amino acid formulas devoid of phenylalanine and enriched in tyrosine with improved palatability have been developed in the last years. These formulas should be given in three daily doses to avoid amino acid overload as well as to minimize losses of L-amino acids by oxidative processes and to minimize fluctuations in phenylalanine concentrations (MacDonald et al. 1996).

The most recent achievement in terms of palatability are glycomacropeptides, proteins derived from cheese whey which is low in phenylalanine and rich in branched-chain amino acids and threonine. Glycomacropeptides have to be supplemented with essential amino acids like tyrosine, tryptophan, arginine, cysteine, and histidine (for an overview, see, e.g., Al Hafid and Christodoulou (2015)).

Possible side effects of phenylalanine-free L-amino acid supplements are gastrointestinal symptoms, proteinuria, and dental caries in some patients (van Wegberg et al. 2017a).

In many countries, PKU is a target disease of newborn mass screening programs; thus treatment can be started just after birth. The amount of phenylalanine in the diet has to be individually titrated; the amount of amino acid formula is calculated based on the recommended daily protein intake. Phenylalanine is essential for protein synthesis and must be provided in an amount that supports growth and tissue repair while keeping plasma phenylalanine concentrations within recommended age-specific ranges for PKU (Macleod and Ney 2010).

Modifications of phenylalanine target levels have recently been proposed (van Spronsen and Derks 2014). Diet for life secures relatively normal life for PKU patients allowing academic careers; however, minor neurological, psychiatric, or behavioral sequelae may be observed in some patients (Koch et al. 2002); long-term outcome in the aging PKU population is still unclear.

In pregnancies of females with PKU ("maternal PKU"), separate, strict treatment recommendations have to be followed to avoid severe fetal and perinatal compromise (Lenke and Levy 1980).

Similar therapeutic principles of low-protein diet supplemented with an amino acid formula devoid of the amino acid(s) which cannot be metabolized due to a missing enzyme are available for maple syrup urine disease (MSUD), hepatorenal tyrosinemia, and organic acidurias (e.g., methylmalonic aciduria, glutaric aciduria, etc.). Some of them are target diseases of the newborn screening in some countries as well.

In recent years, sapropterin, a synthetic analogue of tetrahydrobiopterin BH4, was approved in Europe as a pharmacological chaperone treatment option in PKU patients harboring amenable *PAH* mutations with relatively high residual enzyme activity (see section ▶ "Enzyme Augmentation by Chaperones").

An enzyme 'replacement' therapy is under development (polyethylene glycol phenylalanine ammonia-lyase, PEG-PAL) replacing not the missing enzyme but an enzyme activating an alternative pathway of elimination (see section ▶ "Enzyme Replacement Therapy (ERT)").

Pharmacological Substrate Reduction

Treatment of Hereditary Tyrosinemia Type 1 (Hepatorenal Tyrosinemia, HT-1) by Nitisinone

Hereditary tyrosinemia type 1 (hepatorenal tyrosinemia, HT-1) is a rare inborn error of metabolism in the catabolism of the amino acid tyrosine (Fig. 2).

Biochemically, there is deficiency of fumarylacetoacetase leading to the accumulation not only of tyrosine but of different metabolites like maleylacetoacetate, fumarylacetoacetate, and succinylacetone (SA); the latter is commonly used as a surrogate parameter of toxicity in blood and/or urine (Fig. 2).

Therapy consists of nitisinone (Orfadin®, 2-(2-**n**itro-4**t**rifluoromethyl**b**enzoyl)**c**yclohexane 1-,3-dione (NTBC)) in order to decrease levels of toxic compounds (Fig. 2). Nitisinone blocks the degradation of tyrosine proximal to the enzyme fumarylacetoacetase and prevents the production

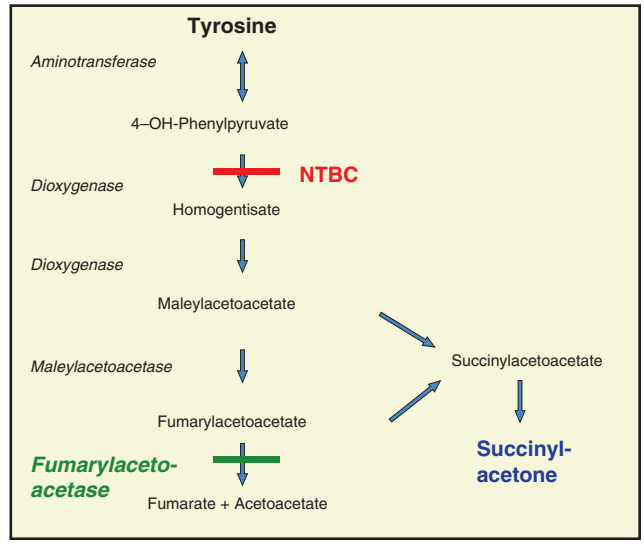

Fig 2 Tyrosinemia is due to deficiency of the enzyme fumarylacetoacetase in the degradative pathway of tyrosine. It results in the accumulation of toxic compounds; succinylacetone is used as a surrogate parameter of toxicity. NTBC (nitisinone) inhibits the enzyme homogentisate dioxygenase with subsequent reduction of toxic metabolites and increased tyrosine levels

of toxic metabolites. A low-protein diet combined with special amino acid mixtures devoid of tyrosine and its precursor phenylalanine is required to prevent excessive tyrosine levels. Nitisinone was approved by the European Medicines Agency (EMA) under exceptional circumstances in 2005. The first clinical use of nitisinone in HT-1 dates back to 1991. Originally, nitisinone was developed as a weed killer by Zeneca Agrochemicals (for a review, see Das AM The Application of Clin Genet 2017). It was epidemiologically observed that growth of plants and weeds was inhibited under the bottlebrush plant (*Callistemon citrinus*). It became clear that neither the shade nor the litterfall of these plants was responsible for suppression of plant and weed growth. Rather a substance, which was identified as leptospermone, in the soil under the bottlebrush plant was shown to have bleaching activity on the emerging plants. The allelochemical leptospermone was extracted from the bottlebrush plant and chemically characterized. It belongs to the triketone family which inhibits chloroplast development due to lack of plastoquinone secondary to hepatic 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibition and served as a blueprint for the synthesis of nitisinone.

Toxicology testing of nitisinone revealed that it was not acutely toxic, but eye lesions (keratopathy) could be observed in animals after longer treatment. Lesions were reversible upon withdrawal of the compound. Elevated tyrosine levels were found in blood and urine after nitisinone exposure. It was established that nitisinone is a potent inhibitor of rat hepatic 4-hydroxyphenylpyruvate dioxygenase (HPPD) at the Zeneca Central Toxicity Laboratories (Fig. 2). Inhibition of human HPPD was demonstrated in the human liver by Sven Lindstedt and his group at Gothenburg University (Sweden). Already for some time, they were looking for an inhibitor of HPPD to treat patients with the lethal disease HT-1. The Zeneca Pharmaceuticals took over the compound as a potential drug though they were reluctant to do so as only a very limited number of patients with this rare disease would possibly benefit from this drug. The Swedish Medical Agency approved a clinical trial with nitisinone in HT-1 patients, and in February 1991, a critically ill 2-month-old baby was the first HT-1 patient treated with nitisinone in Gothenburg. Succinylacetone quickly disappeared from the urine and the clinical state gradually improved. Subsequently, several HT-1 patients were successfully treated with nitisinone on a compassionate use basis. In the following years, many patients were successfully treated with nitisinone culminating in the approval of nitisinone by the US Food and Drug Administration in 2002 and the European Medicines Agency

(EMA) in 2005 under "exceptional circumstances" as large field trials and real-world data in HT-1 patients were lacking. The first sublicense-holder Swedish Orphan International was obliged to perform post-marketing studies which are now carried out by the present sublicense-holder Swedish Orphan Biovitrum (Sobi) in the framework of the "OPAL" study.

In the rat liver, enzyme kinetic studies revealed inhibition of HPPD by nitisinone in a dose- and time-dependent manner with a rate constant of 9.9×10^{-5} s^{-1} $(nmol/L)^{-1}$ (Ellis et al. 1995). Binding of nitisinone to HPPD is not irreversible; the enzyme-inhibitor complex dissociates with a half-life of 63 h in rats at a temperature of 25 °C. Tests in human adult volunteers revealed that the half-life of nitisinone was 54 h (Hall et al. 2001). It is recommended to take nitisinone in two daily doses. However, based on the long half-life of nitisinone, once-daily dosing was advocated (Schlune et al. 2012) which seems to be adequate to maintain metabolic control. Once-daily dosing may improve adherence to pharmacological therapy. However, metabolic control with a once daily dosing regime has been recently questioned (Kienstra et al. 2018).

The recommended dose of nitisinone is 1–2 mg/kg per day given in two doses. In a recent survey (Mayorandan et al. 2014a), we found several HT-1 patients in whom nitisinone was titrated down without hampering metabolic control as judged by the absence of succinylacetone; doses as low as 0.3 mg/kg per day of nitisinone have been shown to be sufficient.

While it is clear that nitisinone can reduce the levels of toxic compounds as judged by the surrogate parameter succinylacetone and secure survival, the impact on long-term clinical outcome is less clear. This is mainly due to the rarity of the disease. In the literature, there is only one multinational cross-sectional study including 168 patients from 21 centers (Mayorandan et al. 2014a). This study showed that there is a clear benefit of nitisinone treatment in combination with low-protein diet supplemented by amino acid mixtures devoid of tyrosine and phenylalanine. If present, liver dysfunction/failure, renal dysfunction, tubulopathy, and rickets could be reversed by nitisinone treatment. Also the rate of HCC could be reduced by nitisinone treatment. Long-term complications, especially HCC formation, critically depend on early initiation of treatment, hence early diagnosis. If treatment is started beyond the first year of life, the risk to develop HCC is 13 times higher compared to a treatment start in the neonatal period, risk for liver cirrhosis is 40-fold, rickets is 19-fold, and tubular dysfunction is 4.3-fold increased (Mayorandan et al. 2014b). Thus, early diagnosis in the newborn period is essential to secure a good long-term outcome.

Neurocognitive deficits are a problem in long-term management (Bendadi et al. 2014; Garcia et al. 2017). It is not clear whether these are direct side effects of nitisinone treatment, are a result of high tyrosine or low phenylalanine levels, or are part of the natural course of the disease. It seems reasonable to reduce nitisinone levels without compromising metabolic control (as judged by succinylacetone in urine and/or blood). Therefore, nitisinone levels should be regularly monitored in dried blood spots, together with succinylacetone (Sander et al. 2011). In most cases, it is possible to titrate down the daily dose of nitisinone from initially 1 mg/kg per day without hampering metabolic control. The tentative therapeutic range of random nitisinone concentration in dried blood is 20–40 μM (Sander et al. 2011).

Gaucher Disease and Eliglustat and Miglustat

Gaucher disease is a rare autosomal recessive storage disorder based on a deficiency of acid ß-glucosidase (glucocerebrosidase). This leads to the storage of glucosylceramide in different organs of the body. Hepatosplenomegaly, bone marrow infiltration with subsequent pancytopenia, bone destruction, and lung disease are common symptoms (Bennett and Mohan 2013). While enzyme replacement therapy (ERT) for M. Gaucher type 1 is available since decades (see section ▶ "Enzyme Replacement Therapy (ERT)"), eliglustat (Cerdelga®) has recently been approved by the US Food and Drug Administration and EMA for pharmacological substrate reduction. Eliglustat is given orally twice daily

and as a ceramide analogue inhibits glucosylceramide synthase (IC 50, 24 nM) (Lukina et al. 2010a). Glucosylceramide synthase is the first enzyme that catalyzes the biosynthesis of glycosphingolipids. Eliglustat is metabolized via cytochrome 450 2D6 and is dosed according to the activity of this enzyme. Favorable safety and efficacy data were observed in several studies before approval was granted. The half-life of eliglustat was 6.8 h (Lukina et al. 2010b), hemoglobin and platelets quickly increased, spleen and liver volumes decreased, and bone crises were less frequent. A specific and sensitive biomarker to evaluate the activity of Gaucher disease is still missing. For M. Gaucher types 2 and 3 (progressive neuropathic forms), no approved drugs are presently available.

Miglustat (Zavesca®) is also approved for the treatment of non-neuronopathic Gaucher disease acting via substrate reduction. Based on the high rate of gastrointestinal side effects of miglustat, eliglustat is preferred by most patients.

Niemann-Pick Type C Disease and Miglustat

M. Niemann-Pick type C (NPC) is an autosomal recessive disorder characterized by impaired trafficking of endocytosed cholesterol with sequestration of unesterified cholesterol in lysosomes and late endosomes (Vanier 2010). Other lipids accumulate as well with variation in different tissues. The disease is due to a defect of the NPC1 (95% of cases) or NPC2 gene. Clinically, visceral organs like liver, spleen, and lungs may be affected; neurological symptoms (clumsiness, learning difficulties, ataxia, dysphagia, dysarthria, vertical gaze palsy) with neurodegeneration are common CNS symptoms.

Substrate reduction using miglustat (Zavesca®) is a disease-modifying therapeutic option, not a cure, probably due to the complexity of the disease pathophysiology with accumulation of many substrates.

Miglustat (deoxynojirimycin) is an iminosugar which reversibly inhibits glycosphingolipid synthesis thus reducing accumulation of glycosphingolipids in NPC (Williamson 2014). This drug can stabilize the clinical course of the disease and may reduce disease progression in some patients. Moderate to severe gastrointestinal side effects (abdominal discomfort, flatulence, and diarrhea) are common and can be ameliorated by modifying the diet (elimination of disaccharides).

Supplementation of a Missing Cofactor/Vitamin

Biotinidase Deficiency

Biotinidase plays a critical role in the uptake of biotin from dietary sources and in biotin recycling. Free biotin enters the biotin cycle from dietary sources or from the cleavage of biocytin or biotinyl peptides by the action of biotinidase. In biotinidase deficiency, an autosomal recessive disease caused by mutations in the *BTD* gene, both deficiencies of biotin and in biotin-dependent carboxylases occur. Treatment with oral administration of free biotin (up to 10 mg per day) can prevent symptoms like cutaneous rash, hair loss, seizures, inner ear hearing loss, and developmental delay. It should ideally be started during the neonatal period to secure complete absence of clinical symptoms after establishing the diagnosis via newborn mass screening. For patients with biotinidase deficiency, newborn screening is a very efficient preventive measure. All individuals with profound biotinidase deficiency, even those who have residual enzyme activity, should be treated with biotin for life. Raw eggs should be avoided because they contain avidin, an egg-white protein that binds biotin and decreases the bioavailability of the vitamin (Wolf 1993).

Metabolic ketolactic acidosis accompanied by organic aciduria (3-hydroxyisovaleric acid may be the only metabolite present) and hyperammonemia are suggestive of biotinidase deficiency; however, urinary organic acids can be normal in symptomatic individuals with biotinidase deficiency.

Cobalamin (Vitamin B12) in Transcobalamin Deficiency and Methylmalonic Aciduria

Cobalamin, also known as vitamin B12, is a water-soluble vitamin that is crucial for the normal

function of the gastrointestinal, dermatologic, immunologic, neuropsychiatric, and hematopoietic systems. The vitamin is essential and must be supplied by diet. Transcobalamin (TCN2) is required to internalize vitamin B12 into the cells through membrane receptor-mediated endocytosis. Vitamin B12 is then processed in the cytoplasm and mitochondria by complementation factors leading to its active metabolites methylcobalamin and 5-deoxyadenosyl-cobalamin.

Deficiency of TCN2 results in an elevation of methylmalonic acid in urine and homocysteine in plasma. Patients usually present with macrocytic anemia, pancytopenia, failure to thrive, gastrointestinal symptoms, and neurological dysfunction. Early detection and early initiation of parenteral vitamin B12 treatment are associated with a better prognosis and disease control (Chao et al. 2017).

Vitamin B12 deficiency due to malnutrition can result in irreversible developmental sequelae. Breast-fed infants from vegan/vegetarian mothers are at risk for vitamin B12 deficiency; this vitamin should be supplemented.

Methylmalonic aciduria is a genetic defect of cobalamin metabolism; several subtypes are known. Some subtypes respond to pharmacological doses of hydroxycobalamin, given intravenously or via intramuscular injection (typically 2–5 mg per day). The vitamin-responsive subtypes mostly have a better long-term outcome (Horster et al. 2007).

N-Carbamylglutamate in N-Acetylglutamatesynthase Deficiency

N-Acetylglutamatesynthase deficiency (estimated incidence, less than 1:2,000,000) is inherited as an autosomal recessive trait and leads to a lack of N-acetylglutamate which serves as a cofactor and allosteric activator of carbamoyl phosphate synthase (CPS1), the first enzymatic step in the urea cycle. N-Carbamylglutamate (carglumic acid, Carbaglu®, Orphan Europe, Paris France, 100–300 mg/kg per day) is a commercially available pharmacological formulation approved by EMA (Summar et al. 2013; Haberle et al. 2012; Haberle 2011).

In some organic acidurias (e.g., methylmalonic aciduria), secondary inhibition of N-acetylglutamatesynthase can occur under poor metabolic control. N-Carbamylglutamate (Carbaglu®) can (partially) compensate this deficiency.

Miscellaneous

Several inborn errors of metabolism respond to vitamins as cofactors of the compromised enzyme. For example, some subtypes of homocystinuria benefit from vitamin B6 and folate, and patients with thiamine-responsive megaloblastic anemia improve under pharmacological therapy with vitamin B1.

Activation of Alternative Pathways for the Elimination of Toxic Compounds

Butyrate and Benzoate in Urea Cycle Defects

Urea cycle defects (UCD) are potentially life-threatening inborn errors of metabolism affecting one of the enzymes involved in the urea cycle. They lead to severe hyperammonemia resulting in encephalopathy, especially during catabolic spells.

Benzoate is conjugated with glycine forming hippurate with one N-atom which, in contrast to ammonia, is water-soluble. Similarly, phenylbutyrate is metabolized to phenylacetate in the liver which then binds glutamine containing two N-atoms. Phenylacetylglutamine is water-soluble; thus two N-atoms can be excreted (Fig. 3). In Europe, no pharmacological benzoate formulation is available; only off-label use of the chemical compound is possible. Sodium phenylbutyrate is available as an oral commercial pharmacological formulation (Ammonaps®); recommended dose is 250–500 mg/kg per day divided in 3–6 doses. Palatability has been improved by carbohydrate coating (Pheburane®). Recently, an alternative, more palatable liquid compound, glycerol phenylbutyrate (Ravicti®), was approved by EMA (Diaz et al. 2013). If required, phenylacetate can be given intravenously; if liver function is intact, this compound is metabolized to phenylbutyrate.

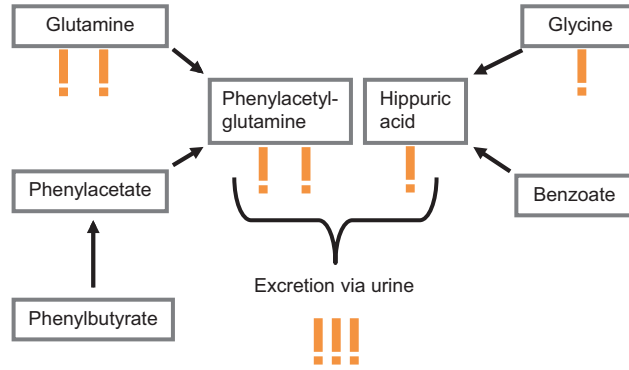

Fig. 3 Use of scavengers in urea cycle defects: Phenylacetate binds glutamine with two N-atoms (orange) with the formation of phenylacetylglutamate which is water-soluble. Benzoate bind glycine (one N-atom) resulting in the production of hippurate which is water-soluble and can be excreted via urine

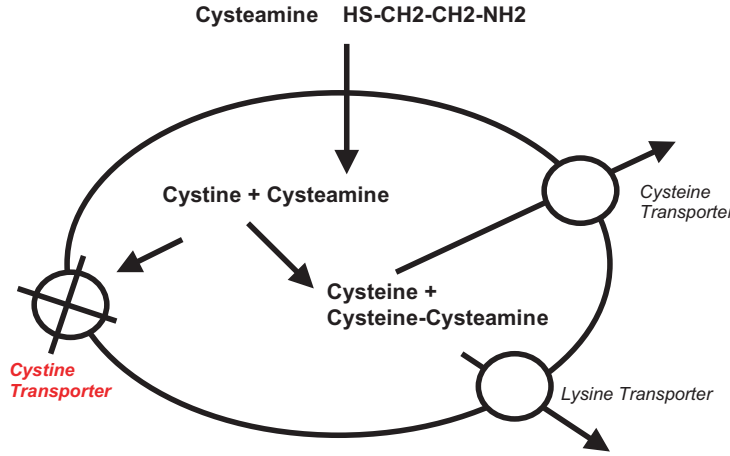

Fig. 4 Cystinosis is due to deficiency of the cystine transporter. Cysteamine binds cystine leading to cysteine and cysteine-cysteamine which are transported out of the lysosomes via the cysteine transporter and the lysine transporter, respectively

Benzoate in Nonketotic Hyperglycinemia

Nonketotic hyperglycinemia (NKH) is an inherited defect of the glycine cleavage system leading to the accumulation of glycine with a local production of glycine in the CNS. The CNS/plasma ratio is elevated. Clinically, the patients suffer from encephalopathy with severe epilepsy and psychomotor retardation. As mentioned above (section ▶ "Butyrate and Benzoate in Urea Cycle Defects"), benzoate can bind glycine leading to water-soluble hippurate which can be eliminated via urine. Clinically, this therapeutic option has only a minor effect in most patients (Boneh et al. 2008).

Cysteamine in Cystinosis

Cystinosis is an autosomal recessive storage disease due to mutations of the cystinosin gene which results in the dysfunction of the lysosomal transporter cystinosin. As a result of this dysfunction, cystine accumulates in lysosomes leading to clinical symptoms like nephropathy (predominantly tubulopathy) mostly culminating in renal failure, growth retardation, corneal crystals, endocrinological abnormalities, sometimes hepatosplenomegaly, severe myopathy, and CNS symptoms in adulthood (for a recent review, see Veys et al. (2017)).

Treatment consists of activating alternative pathways for the transport of cystine out of the lysosomes (Fig. 4). Since the mid-1990s, immediate-release cysteamine bitartrate (Cystagon®) at a dose of 1.3 g/m^2 per day (divided in four doses per day) was the only therapeutic option for many years delaying the progress of disease. A serious side effect of this therapy is halitosis and poor taste which hampers compliance. In the last decade, a new extended-release formulation of cysteamine bitartrate (PROCYSBI®) was developed which shall be taken at 80% of the daily

Cystagon® dose, divided in two servings. Immediate- and delayed-release preparations were compared in a crossover study (Langman et al. 2012). Pharmacokinetic data have been measured in the crossover study, $t_{1/2}$ was 254 min in the delayed-release preparation; Cmax 3.7 mg/l and $AUC_{0\text{-}12h}$ were 739 min x mg/l compared to 90 min, 2.7 mg/l and 357 min x mg/l in the immediate-release preparation, respectively. The new formulation has improved compliance; halitosis seems to be reduced (Franke et al. 2017); however, this formulation is much more expensive than the immediate-release product.

The cystine-depleting therapy is monitored by analyzing cystine content in leukocytes using high-performance liquid chromatography.

Oral cystine-depleting medication does not affect formation of corneal cystine crystals in the eyes. Therefore, topical cysteamine hydrochloride preparations have to be administered to control ophthalmological symptoms. Cystaran® eye drops containing 0.44% cysteamine hydrochloride are approved in the USA, while Cystadrops® (0.55% cysteamine hydrochloride) was approved in 2016 in Europe by the EMA (Labbe et al. 2014).

Enzyme Augmentation by Chaperones

Sapropterin Dihydrochloride and Phenylketonuria

Tetrahydrobiopterin (6R-tetrahydrobiopterin, BH4) is the natural cofactor of phenylalanine hydroxylase, the enzyme deficient in classical phenylketonuria (PKU). Some mutants in mild PKU can be stabilized by BH4 leading to an increase in the residual activity of phenylalanine hydroxylase, hence an increased protein tolerance. This can have a positive impact on the quality of life in these patients (Burton et al. 2010). BH4 responsiveness should be determined individually with respect to improvement in biochemical control and increase in natural protein intake. Thus, BH4 acts as a chaperone. Sapropterin dihydrochloride is now available as a pharmaceutical formulation (Kuvan®, marketed by BioMarin) of the natural cofactor BH4; approval of the drug for patients younger than 4 years has only recently been granted by EMA. In young children, elimination half-life was calculated at about 1 h, absorption half-life was 3 h, absorption was rate-limiting for disposition, and once-daily dosing was reported to be adequate (Muntau et al. 2017). The recommended dose is 10 mg/kg once daily. While blood phenylalanine levels can be reduced by about 30% in amenable mutations, about 20% of PKU patients respond to this therapeutic option (Heintz et al. 2013). This compound is tolerated well; there are no serious short-term side effects (Longo et al. 2015); however, long-term safety has still to be assessed as BH4 is also a cofactor for other enzymes (e.g., NO synthase).

The cost-effectiveness of Kuvan® is not established, especially when dietary treatment and phenylalanine-free L-amino acid supplements are still required (Longo et al. 2015; Shintaku and Ohura 2014); a detailed health technology assessment is required.

Migalastat and Fabry Disease

Fabry disease (also known as Anderson disease, OMIM 301500) is an X-linked lysosomal storage disorder caused by a deficiency in the activity of alpha-galactosidase A. Symptoms are usually more severe in males compared to females based on X-chromosomal inheritance. Clinically, M. Fabry is a multisystemic disease affecting the skin, heart, kidney, brain, peripheral nervous system, gastrointestinal tract, ear, eye, endocrinological system, etc. Globotriaosylceramide (Gb3) is the accumulating substance and can be used as a biomarker, together with lyso-Gb3 (globotriaosylsphingosine) which can be measured in blood and/or urine. Typical clinical symptoms are angiokeratoma, acroparesthesia, hypohydrosis, cornea verticillata, hearing difficulties, vertigo, progressive vascular disease of the heart and kidney, hypothyroidism, diarrhea, and psychiatric symptoms; however, in some patients, clinical manifestations are limited to the heart or kidney.

Since 2001, enzyme replacement therapy (Fabrazyme® and Replagal®) is available (see section ▶ "Enzyme Replacement Therapy (ERT)") which leads to improvement of

symptoms in many, but not all, patients; however, symptoms do not disappear completely. The brain is not accessible to this treatment option based on the blood-brain barrier (e.g., Lidove et al. 2016). This therapeutic intervention is challenging, intravenous therapy has to be given every other week over several hours, and immunological processes may lead to allergic or even anaphylactic reactions. In some patients, neutralizing antibodies may form which renders therapy ineffective. Based on a short half-live of the infused enzyme, fluctuation of clinical symptoms is often reported by the patients.

Some mutations are amenable to oral pharmacological chaperone therapy by migalastat (1-deoxygalactonojirimycin, Galafold®) by stabilizing protein folding. The mutated, misfolded enzyme is retained in the endoplasmic reticulum and prematurely degraded. Intracellular processing can be restored by migalastat in some mutations (Ishii et al. 2007; Ishii 2012) where proper folding can be induced. Preliminary studies and pharmacokinetic and safety studies were performed in healthy volunteers showing that migalastat is rapidly absorbed and up to 60% of migalastat can be recovered unchanged in urine, the half-life was approximately 4 h in plasma, and no serious side effects were observed (Johnson et al. 2013).

Subsequent phase 2 studies on safety and pharmacodynamic effects of migalastat were performed in adult male patients demonstrating safety and efficacy in terms of increased alpha-galactosidase activity and reduced Gb3 levels not only in plasma and urine but also in the skin and kidney (Germain et al. 2012). Based on a lysosomal half-life of 110–120 h (Benjamin et al. 2009), migalastat was given every other day. Another phase 2 study was performed in females with amenable and non-amenable mutations showing that migalastat is well tolerated and shows efficacy in patients with amenable mutations (Giugliani et al. 2013).

Galafold® has been approved by the European Medicines Agency (EMA) in 2016 for the use in patients with Fabry disease older than 16 years carrying an amenable mutation. Amenability of mutations is based on in vitro testing; a continuously updated list on amenable mutations can be found at www.GalafoldAmenabilityTable.com.

Despite these advances in therapy of Fabry patients, there are limitations of chemical chaperones in clinical practice. They are mutation specific and therefore only selected patients are responsive. Furthermore, chemical chaperones bind to the catalytic site of the enzymes with the risk that they impair activity instead of enhancing it if given at high doses and/or more often than required.

Enzyme Replacement Therapy (ERT)

Enzyme Replacement Therapy (ERT) in Selected Lysosomal Storage Diseases

Deficiency of lysosomal enzymes will lead to the accumulation of complex lysosomal molecules like glycogen in patients suffering from Pompe disease, glycosaminoglycans in cases of mucopolysaccharidoses (for instance, Morbus Hurler, MPS 1), glycoproteins in patients suffering from oligosaccharidoses (like Morbus Fabry), and sphingolipids in cases of Niemann-Pick disease types A and B, Gaucher disease, as well as cerebral lysosomal diseases like Tay-Sachs disease, Krabbe disease, and metachromatic leukodystrophy (Ferreira and Gahl 2017).

Sebelipase alfa (Kanuma®) is a recombinant human lysosomal acid lipase (LAL) approved for the treatment of LAL deficiency (Wolman disease) (Frampton 2016).

Asfotase alfa (Strensiq®) is a human recombinant enzyme replacement therapy for patients suffering from hypophosphatasia (Whyte 2017).

The goal of ERT is to compensate metabolic defects in patients with lysosomal storage disease by regular intravenous infusions of recombinant enzymes (every week or every other week depending on the underlying disorder). Classically, the enzyme is produced in bioreactors using human fibroblasts or Chinese hamster ovary cells as starter cultures. Biotechnologically produced enzymes are coupled to mannose 6-phosphate or mannose 6-phosphate is exposed as a signal substance. By virtue of the mannose-6-phosphate receptor at the cell surface, the intravenously

applied enzymes can be taken up by cells and transported to the lysosomes where they take over catalytic functions. Storage material will be degraded by this treatment leading to clinical improvement of some but not all organ functions. The central nervous system does not benefit from intravenous ERT due to the blood-brain barrier; bradytrophic tissues poorly respond to ERT. In addition, the therapeutic effect may be hampered by the development of antibodies against recombinant enzymes leading to complete inefficacy of ERT (Banugaria et al. 2011).

To deliver recombinant enzyme to the brain, intrathecal infusion was performed in a phase 1/phase 2 study in 12 patients with MPS IIIA (Sanfilippo disease A) (Jones et al. 2016); results were not convincing. Alternatively to this invasive procedure, enzymes have been modified to facilitate crossing of the blood-brain barrier by fusion to a monoclonal antibody against the human insulin receptor, called HIRMAb (Boado et al. 2014).

In the last years, enzyme replacement therapy has become available for a number of lysosomal storage diseases: imiglucerase (Cerezyme®), taliglucerase (Elelyso®, not approved in Europe), and velaglucerase (VIPRIV®) for Gaucher disease type 1, laronidase (Aldurazyme®) for Hurler disease (MPS type 1), idursulfase (Elaprase®) for Hunter disease (MPS type 2), elosulfase alfa (Vimizim®) for Morquio disease (MPS type 4), galsulfase (Naglazyme®) for Maroteaux-Lamy disease (MPS type 6), alglucosidase alfa (Myozyme®) for Pompe disease (glycogen storage disease type 2), and agalsidase alfa (Replagal®) and beta (Fabrazyme®) for Fabry disease. For patients suffering from Niemann-Pick disease types A and B, a recombinant human acid sphingomyelinase (olipudase alpha) is currently tested in clinical trials as an intravenous enzyme replacement therapy (Wasserstein et al. 2015).

ERT in lysosomal storage disorders is costly and requires a multi-professional approach which makes this therapeutic option logistically and economically challenging (Das et al. 2017).

Patients with lysosomal storage disorders are generally normal at birth, with symptoms developing in the first year(s) of life.

Many different cell types and tissues are affected by lysosomal storage disorders, with involvement at different stages in the disease process. ERT cannot cure patients but can stabilize organ function or slow progression.

A new biotechnology for large-scale production of enzymes that can be used for ERT is moss-based. Alpha-galactosidase A produced by the moss *Physcomitrella patens* was successfully used as an ERT in Fabry mice (Reski et al. 2015). Cellular uptake of the deficient enzyme occurs via mannose receptors after mannose-terminated enzymes bind to these receptors. Enzyme concentrations of 10 μg/ml were used; dose-dependent uptake of the enzyme up to 40 μg/ml was observed. One advantage of moss-based ERT is a higher homogeneity and reproducibility of enzyme glycosylation compared to mammalian cell-based ERT (Shen et al. 2016).

Compared with ERT, substrate reduction therapy or chaperone therapy in lysosomal storage diseases (see above) has some advantages as these small molecules can be given orally, they do not generate immune reactions, and they have the potential to cross the blood-brain barrier. However, this therapeutic option is currently only available for M. Gaucher type 1 (eliglustat) and Morbus Niemann-Pick type C (miglustat) and as a chaperone therapy in M. Fabry (migalastat).

Enzyme Replacement Therapy by Phenylalanine Ammonia Lyase in Phenylketonuria

As mentioned above, patients with classical PKU have a compromised activity of phenylalanine hydroxylase, the enzyme that catalyzes the irreversible conversion of phenylalanine to tyrosine. In the absence of treatment, systemic phenylalanine concentrations can increase to neurotoxic levels and impair cognitive development. The treatment of PKU requires lifelong selective reduction of phenylalanine intake and an adequate dietary supply of tyrosine by a protein-restricted diet supplemented with special amino acid mixtures devoid of phenylalanine and enriched with tyrosine. Adherence to this restricted diet is often challenging.

A possible enzyme 'replacement' therapy using PEG phenylalanine ammonia-lyase (PEG-PAL) or Pegvaliase® subcutaneously is under investigation. This enzyme converts phenylalanine to ammonia and trans-cinnamic acid. PEG-PAL clinical phase 2 trials have proven short-term reduction in the blood phenylalanine concentrations in adult PKU patients, but further studies are required to assess long-term efficacy and safety. Results of a phase 3 extension study (NCT01819727) are awaited. Therefore, phenylalanine ammonia lyase as a non-mammalian protein providing alternative phenylalanine metabolism has the potential to relief dietary restrictions and secure a better quality of life in the long run; however, tyrosine remains an essential amino acid which has to be supplemented (Longo et al. 2014; van Wegberg et al. 2017b).

Outlook

Taken together, different therapeutic principles can improve clinical outcome in patients suffering from IEM. These options interfere with the pathophysiology of disease based on the underlying biochemical defect. By better understanding the pathobiochemistry of IEMs, more therapeutic options will become available. Individualized medicine in the field of IEM will improve efficacy and reduce side effects.

As IEMs are monogenetic diseases, genetic correction will be a further milestone beyond pharmacological therapy.

References and Further Reading

Al Hafid N, Christodoulou J (2015) Phenylketonuria: a review of current and future treatments. Transl Pediatr 4(4):304–317. https://doi.org/10.3978/j.issn.2224-4336.2015.10.07

Banugaria SG, Prater SN, Ng YK, Kobori JA, Finkel RS, Ladda RL, Chen YT, Rosenberg AS, Kishnani PS (2011) The impact of antibodies on clinical outcomes in diseases treated with therapeutic protein: lessons learned from infantile Pompe disease. Genet Med 13(8):729–736. https://doi.org/10.1097/GIM.0b013e3182174703

Bendadi F, de Koning TJ, Visser G, Prinsen HC, de Sain MG, Verhoeven-Duif N, Sinnema G, van Spronsen FJ, van Hasselt PM (2014) Impaired cognitive functioning in patients with tyrosinemia type I receiving nitisinone. J Pediatr 164(2):398–401. https://doi.org/10.1016/j.jpeds.2013.10.001

Benjamin ER, Flanagan JJ, Schilling A, Chang HH, Agarwal L, Katz E, Wu X, Pine C, Wustman B, Desnick RJ, Lockhart DJ, Valenzano KJ (2009) The pharmacological chaperone 1-deoxygalactonojirimycin increases alpha-galactosidase a levels in Fabry patient cell lines. J Inherit Metab Dis 32(3):424–440. https://doi.org/10.1007/s10545-009-1077-0

Bennett LL, Mohan D (2013) Gaucher disease and its treatment options. Ann Pharmacother 47(9):1182–1193. https://doi.org/10.1177/1060028013500469

Bickel H, Gerrard J, Hickmans EM (1954) The influence of phenylalanine intake on the chemistry and behaviour of a phenyl-ketonuric child. Acta Paediatr 43(1):64–77

Blau N, van Spronsen FJ, Levy HL (2010) Phenylketonuria. Lancet 376(9750):1417–1427. https://doi.org/10.1016/S0140-6736(10)60961-0

Boado BJ, Ka-Wai Hui E, Lu JZ, Pardridge WM, (2014) Insulin receptor antibody-iduronate 2-sulfatase fusion protein: Pharmacokinetics, anti-drug antibody, and safety pharmacology in Rhesus monkeys. Biotechnol Bioeng 111(11):2317–2325

Boneh A, Allan S, Mendelson D, Spriggs M, Gillam LH, Korman SH (2008) Clinical, ethical and legal considerations in the treatment of newborns with non-ketotic hyperglycinaemia. Mol Genet Metab 94(2):143–147. https://doi.org/10.1016/j.ymgme.2008.02.010

Burton BK, Bausell H, Katz R, Laduca H, Sullivan C (2010) Sapropterin therapy increases stability of blood phenylalanine levels in patients with BH4-responsive phenylketonuria (PKU). Mol Genet Metab 101(2–3):110–114. https://doi.org/10.1016/j.ymgme.2010.06.015

Chao MM, Illsinger S, Yoshimi A, Das AM, Kratz CP (2017) Congenital Transcobalamin II deficiency: a rare entity with a broad differential. Klin Padiatr 229 (6):335–357. https://doi.org/10.1055/s-0043-120266

Christ SE (2003) Asbjorn Folling and the discovery of phenylketonuria. J Hist Neurosci 12(1):44–54

Das AM, Lagler F, Beck M, Scarpa M, Lampe C (2017) Lysosomal storage diseases: challenges in multiprofessional patient care with enzyme replacement therapy. Klin Padiatr 229(3):168–174. https://doi.org/10.1055/s-0043-103088

Diaz GA, Krivitzky LS, Mokhtarani M, Rhead W, Bartley J, Feigenbaum A, Longo N, Berquist W, Berry SA, Gallagher R, Lichter-Konecki U, Bartholomew D, Harding CO, Cederbaum S, McCandless SE, Smith W, Vockley G, Bart SA, Korson MS, Kronn D, Zori R, Merritt JL 2nd, C S Nagamani S, Mauney J, Lemons C, Dickinson K, Moors TL, Coakley DF, Scharschmidt BF, Lee B (2013) Ammonia control and neurocognitive outcome among urea cycle disorder patients treated with glycerol phenylbutyrate. Hepatology 57 (6):2171–2179. https://doi.org/10.1002/hep.26058

Ellis MK, Whitfield AC, Gowans LA, Auton TR, Provan WM, Lock EA, Smith LL (1995) Inhibition of 4-hydroxyphenylpyruvate dioxygenase by 2-(2-nitro-4-

trifluoromethylbenzoyl)-cyclohexane-1,3-dione and 2-(2-chloro-4-methanesulfonylbenzoyl)-cyclohexane-1,3-dione. Toxicol Appl Pharmacol 133(1):12–19. https://doi.org/10.1006/taap.1995.1121

Ferreira CR, Gahl WA (2017) Lysosomal storage diseases. Transl Sci Rare Dis 2(1–2):1–71. https://doi.org/10.3233/TRD-160005

Frampton JE (2016) Sebelipase alfa: a review in lysosomal acid lipase deficiency. Am J Cardiovasc Drugs 16 (6):461–468. https://doi.org/10.1007/s40256-016-0203-2

Franke D, Steffens R, Thomas L, Pavicic L, Ahlenstiel T, Pape L, Gellermann J, Müller D, Querfeld U, Haffner D, Zivicnjak M (2017) Kidney transplantation fails to provide adequate growth in children with chronic kidney disease born small for gestational age. Pediatr Nephrol 32(3):511–519. https://doi.org/10.1007/s00467-016-3503-5

Garcia MI, de la Parra A, Arias C, Arredondo M, Cabello JF (2017) Long-term cognitive functioning in individuals with tyrosinemia type 1 treated with nitisinone and protein-restricted diet. Mol Genet Metab Rep 11:12–16. https://doi.org/10.1016/j.ymgmr.2017.01.016

Garrod AE (1902) About Alkaptonuria. Med Chir Trans 85:69–78

Germain DP, Giugliani R, Hughes DA, Mehta A, Nicholls K, Barisoni L, Jennette CJ, Bragat A, Castelli J, Sitaraman S, Lockhart DJ, Boudes PF (2012) Safety and pharmacodynamic effects of a pharmacological chaperone on alpha-galactosidase a activity and globotriaosylceramide clearance in Fabry disease: report from two phase 2 clinical studies. Orphanet J Rare Dis 7:91. https://doi.org/10.1186/1750-1172-7-91

Giugliani R, Waldek S, Germain DP, Nicholls K, Bichet DG, Simosky JK, Bragat AC, Castelli JP, Benjamin ER, Boudes PF (2013) A phase 2 study of migalastat hydrochloride in females with Fabry disease: selection of population, safety and pharmacodynamic effects. Mol Genet Metab 109(1):86–92. https://doi.org/10.1016/j.ymgme.2013.01.009

Haberle J (2011) Role of carglumic acid in the treatment of acute hyperammonemia due to N-acetylglutamate synthase deficiency. Ther Clin Risk Manag 7:327–332. https://doi.org/10.2147/TCRM.S12703

Haberle J, Boddaert N, Burlina A, Chakrapani A, Dixon M, Huemer M, Karall D, Martinell D, Crespo PS, Santer R, Servais A, Valayannopoulos V, Linder M, Rubio V, Dionisi-Vici C (2012) Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet J Rare Dis 7:32. https://doi.org/10.1186/1750-1172-7-32

Hall MG, Wilks MF, Provan WM, Eksborg S, Lumholtz B (2001) Pharmacokinetics and pharmacodynamics of NTBC (2-(2-nitro-4-fluoromethylbenzoyl)-1,3-cyclohexanedione) and mesotrione, inhibitors of 4-hydroxyphenyl pyruvate dioxygenase (HPPD) following a single dose to healthy male volunteers. Br J Clin Pharmacol 52(2):169–177

Heintz C, Cotton RG, Blau N (2013) Tetrahydrobiopterin, its mode of action on phenylalanine hydroxylase, and importance of genotypes for pharmacological therapy of phenylketonuria. Hum Mutat 34(7):927–936. https://doi.org/10.1002/humu.22320

Horster F, Baumgartner MR, Viardot C, Suormala T, Burgard P, Fowler B, Hoffmann GF, Garbade SF, Kölker S, Baumgartner ER (2007) Long-term outcome in methylmalonic acidurias is influenced by the underlying defect (mut0, Mut-, cblA, cblB). Pediatr Res 62 (2):225–230. https://doi.org/10.1203/PDR.0b013e3180a0325f

Ishii S (2012) Pharmacological chaperone therapy for Fabry disease. Proc Jpn Acad Ser B Phys Biol Sci 88 (1):18–30

Ishii S, Chang HH, Kawasaki K, Yasuda K, Wu HL, Garman SC, Fan JQ (2007) Mutant alpha-galactosidase a enzymes identified in Fabry disease patients with residual enzyme activity: biochemical characterization and restoration of normal intracellular processing by 1-deoxygalactonojirimycin. Biochem J 406(2):285–295. https://doi.org/10.1042/BJ20070479

Johnson FK, Mudd PN Jr, Bragat A, Adera M, Boudes P (2013) Pharmacokinetics and safety of Migalastat HCl and effects on Agalsidase activity in healthy volunteers. Clin Pharmacol Drug Dev 2(2):120–132. https://doi.org/10.1002/cpdd.1

Jones SA, Breen C, Heap F, Rust S, de Ruijter J, Tump E, Marchal JP, Qiu Y, Chung JK, Nair N, Haslett PA, Wijburg FA (2016) A phase 1/2 study of intrathecal heparan-N-sulfatase in patients with mucopolysaccharidosis IIIA. Mol Genet Metab 118(3):198–205. https://doi.org/10.1016/j.ymgme.2016.05.006

Kienstra NS, van Reemst HE, van Ginkel VG, Daly A, van Dam E, MacDonald A, Burgerhof JGM, de Blaauw P, McKiernan PJ, Rebecca Heiner-Fokkema M, van Spronsen FJ (2018) Daily variation of NTBC and its relation to succinylacetone in tyrosinemia type 1 patients comparing a single dose to two doses a day. J Inherit Metab Dis 41(2):181–186

Koch R, Burton B, Hoganson G, Peterson R, Rhead W, Rouse B, Scott R, Wolff J, Stern AM, Guttler F, Nelson M, de la Cruz F, Coldwell J, Erbe R, Geraghty MT, Shear C, Thomas J, Azen C (2002) Phenylketonuria in adulthood: a collaborative study. J Inherit Metab Dis 25 (5):333–346

Labbe A, Baudouin C, Deschenes G, Loirat C, Charbit M, Guest G, Niaudet P (2014) A new gel formulation of topical cysteamine for the treatment of corneal cystine crystals in cystinosis: the Cystadrops OCT-1 study. Mol Genet Metab 111(3):314–320. https://doi.org/10.1016/j.ymgme.2013.12.298

Langman CB, Greenbaum LA, Sarwal M, Grimm P, Niaudet P, Deschênes G, Cornelissen E, Morin D, Cochat P, Matossian D, Gaillard S, Bagger MJ, Rioux P (2012) A randomized controlled crossover trial with delayed-release cysteamine bitartrate in nephropathic cystinosis: effectiveness on white blood cell cystine levels and comparison of safety. Clin J Am Soc Nephrol 7(7):1112–1120. https://doi.org/10.2215/CJN.12321211

Lenke RR, Levy HL (1980) Maternal phenylketonuria and hyperphenylalaninemia. An international survey of the outcome of untreated and treated pregnancies. N Engl J Med 303(21):1202–1208. https://doi.org/10.1056/NEJM198011203032104

Lidove O, Barbey F, Joly D (2016) Treatment of Fabry disease: successes, failures, and expectations. Nephrol Ther 12(Suppl 1):105–113. https://doi.org/10.1016/j.nephro.2016.02.003

Longo N, Harding CO, Burton BK, Grange DK, Vockley J, Wasserstein M, Rice GM, Dorenbaum A, Neuenburg JK, Musson DG, Gu Z, Sile S (2014) Single-dose, subcutaneous recombinant phenylalanine ammonia lyase conjugated with polyethylene glycol in adult patients with phenylketonuria: an open-label, multicentre, phase 1 dose-escalation trial. Lancet 384 (9937):37–44. https://doi.org/10.1016/S0140-6736(13)61841-3

Longo, N., Arnold, G. L., Pridjian, G., Enns, G. M., Ficicioglu, C., Parker, S.,. .. Safety, R. (2015). Long-term safety and efficacy of sapropterin: the PKUDOS registry experience. Mol Genet Metab, 114(4), 557–563. https://doi.org/10.1016/j.ymgme.2015.02.003

Lukina E, Watman N, Arreguin EA, Dragosky M, Iastrebner M, Rosenbaum H, Phillips M, Pastores GM, Kamath RS, Rosenthal DI, Kaper M, Singh T, Puga AC, Peterschmitt MJ (2010a) Improvement in hematological, visceral, and skeletal manifestations of Gaucher disease type 1 with oral eliglustat tartrate (Genz-112638) treatment: 2-year results of a phase 2 study. Blood 116(20):4095–4098. https://doi.org/10.1182/blood-2010-06-293902

Lukina E, Watman N, Arreguin EA, Banikazemi M, Dragosky M, Iastrebner M, Rosenbaum H, Phillips M, Pastores GM, Rosenthal DI, Kaper M, Singh T, Puga AC, Bonate PL, Peterschmitt MJ (2010b) Improvement in hematological, visceral, and skeletal manifestations of Gaucher disease type 1 with oral eliglustat tartrate (Genz-112638) treatment: 2-year results of a phase 2 study. Blood 116(20):4095–4098. https://doi.org/10.1182/blood-2010-06-293902

MacDonald A, Rylance G, Hall SK, Asplin D, Booth IW (1996) Factors affecting the variation in plasma phenylalanine in patients with phenylketonuria on diet. Arch Dis Child 74(5):412–417

Macleod EL, Ney DM (2010) Nutritional Management of Phenylketonuria. Ann Nestle Eng 68(2):58–69. https://doi.org/10.1159/000312813

Mayorandan, S., Meyer, U., Gokcay, G., Segarra, N. G., de Baulny, H. O., van Spronsen, F.,. .. Das, A. M. (2014a). Cross-sectional study of 168 patients with hepatorenal tyrosinaemia and implications for clinical practice. Orphanet J Rare Dis, 9, 107. https://doi.org/10.1186/s13023-014-0107-7

Mayorandan S, Meyer U, Hartmann H, Das AM (2014b) Glycogen storage disease type III: modified Atkins diet improves myopathy. Orphanet J Rare Dis 9:196. https://doi.org/10.1186/s13023-014-0196-3

Muntau AC, Burlina A, Eyskens F, Freisinger P, De Laet C, Leuzzi V, Rutsch F, Serap Sivri H, Vijay S, Bal MO, Gramer G, Pazdírková R, Cleary M, Lotz-Havla AS, Munafo A, Mould DR, Moreau-Stucker F, Rogoff D (2017) Efficacy, safety and population pharmacokinetics of sapropterin in PKU patients <4 years: results from the SPARK open-label, multicentre, randomized phase IIIb trial. Orphanet J Rare Dis 12(1):47. https://doi.org/10.1186/s13023-017-0600-x

Reski R, Parsons J, Decker EL (2015) Moss-made pharmaceuticals: from bench to bedside. Plant Biotechnol J 13(8):1191–1198. https://doi.org/10.1111/pbi.12401

Sander J, Janzen N, Terhardt M, Sander S, Gokcay G, Demirkol M, Ozer I, Peter M, Das AM (2011) Monitoring tyrosinaemia type I: blood spot test for nitisinone (NTBC). Clin Chim Acta 412(1–2):134–138. https://doi.org/10.1016/j.cca.2010.09.027

Schlune A, Thimm E, Herebian D, Spiekerkoetter U (2012) Single dose NTBC-treatment of hereditary tyrosinemia type I. J Inherit Metab Dis 35(5):831–836. https://doi.org/10.1007/s10545-012-9450-9

Shen J-S, Busch A, Day TS, Meng X-L, Chun IY, Dabrowska-Schlepp P, Fode B, Niederkrüger H, Forni S, Chen S, Schiffmann R, Frischmuth T, Schaaf A (2016) Mannose receptor-mediated delivery of moss-made alpha-galactosidase a efficiently corrects enzyme deficiency in Fabry mice. J Inherit Metab Dis 39 (2):293–303. https://doi.org/10.1007/s10545-015-9886-9

Shintaku H, Ohura T (2014) Sapropterin is safe and effective in patients less than 4-years-old with BH4-responsive phenylalanine hydrolase deficiency. J Pediatr 165(6):1241–1244. https://doi.org/10.1016/j.jpeds.2014.08.003

Summar ML, Koelker S, Freedenberg D, Le Mons C, Haberle J, Lee HS, Kirmse B (2013) The incidence of urea cycle disorders. Mol Genet Metab 110 (1–2):179–180. https://doi.org/10.1016/j.ymgme.2013.07.008

van Spronsen FJ, Derks TG (2014) Recombinant phenylalanine ammonia lyase in phenylketonuria. Lancet 384 (9937):6–8. https://doi.org/10.1016/S0140-6736(13)62075-9

van Wegberg AMJ, MacDonald A, Ahring K, Belanger-Quintana A, Blau N, Bosch AM, Burlina A, Campistol J, Feillet F, Gizewska M, Huijbregts SC, Kearney S, Leuzzi V, Maillot F, Muntau AC, van Rijn M, Trefz F, Walter JH, van Spronsen FJ (2017a) The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis 12(1):162. https://doi.org/10.1186/s13023-017-0685-2

van Wegberg AMJ, MacDonald A, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, Burlina A, Campistol J, Feillet F, Giżewska M, Huijbregts SC, Kearney S, Leuzzi V, Maillot F, Muntau AC, van Rijn M, Trefz F, Walter JH, van Spronsen FJ (2017b) The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis 12(1):162. https://doi.org/10.1186/s13023-017-0685-2

Vanier MT (2010) Niemann-pick disease type C. Orphanet J Rare Dis 5:16. https://doi.org/10.1186/1750-1172-5-16

Veys KR, Elmonem MA, Arcolino FO, van den Heuvel L, Levtchenko E (2017) Nephropathic cystinosis: an update. Curr Opin Pediatr 29(2):168–178. https://doi.org/10.1097/MOP.0000000000000462

Wasserstein MP, Jones SA, Soran H, Diaz GA, Lippa N, Thurberg BL, Culm-Merdek K, Shamiyeh E, Inguilizan H, Cox GF, Puga AC (2015) Successful within-patient dose escalation of olipudase alfa in acid sphingomyelinase deficiency. Mol Genet Metab 116(1–2):88–97. https://doi.org/10.1016/j.ymgme.2015.05.013

Whyte MP (2017) Hypophosphatasia: enzyme replacement therapy brings new opportunities and new challenges. J Bone Miner Res 32(4):667–675. https://doi.org/10.1002/jbmr.3075

Williamson L (2014) Counterfeit drugs are everyone's business. Krankenpfl Soins Infirm 107(7):72–73

Wolf B (1993) Biotinidase Deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A (eds) GeneReviews((R)). University of Washington, Seattle