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LEADING ARTICLE

Long-Term Outcomes and Practical Considerations in the Pharmacological Management of Tyrosinemia Type 1

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Abstract

Tyrosinemia type 1 (TT1) is a rare metabolic disease caused by a defect in tyrosine catabolism. TT1 is clinically characterized by acute liver failure, development of hepatocellular carcinoma, renal and neurological problems, and consequently an extremely poor outcome. This review showed that the introduction of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) in 1992 has revolutionized the outcome of TT1 patients, especially when started pre-clinically. If started early, NTBC can prevent liver failure, renal problems, and neurological attacks and decrease the risk for hepatocellular carcinoma. NTBC has been shown to be safe and well tolerated, although the long-term effectiveness of treatment with NTBC needs to be awaited. The high tyrosine concentrations caused by treatment with NTBC could result in ophthalmological and skin problems and requires life-long dietary restriction of tyrosine and its precursor phenylalanine, which could be strenuous to adhere to. In addition, neurocognitive problems have been reported since the introduction of NTBC, with hypothesized but as yet unproven pathophysiological mechanisms. Further research should be done to investigate the possible relationship between important clinical outcomes and blood concentrations of biochemical parameters such as phenylalanine, tyrosine, succinylacetone, and NTBC, and to develop clear guidelines for treatment and follow-up with reliable measurements. This all in order to ultimately improve the combined NTBC and dietary treatment and limit possible complications such as hepatocellular carcinoma development, neurocognitive problems, and impaired quality of life.

Key Points

Treatment with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) has been found to be generally safe and has clearly improved treatment and outcomes for patients with tyrosinemia type 1.

The long-term risks for complications associated with tyrosinemia type 1 or treatment with NTBC are not yet fully known and therefore strict follow-up is necessary.

Future challenges include the development of uniform guidelines for treatment and follow-up, and weighing the risks, challenges, and costs of existing and alternative strategies for the treatment of tyrosinemia type 1.

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1 Introduction

Tyrosinemia type 1 (TT1; OMIM276700), also called hepatorenal tyrosinemia, is an inborn error of metabolism, caused by an autosomal recessive inherited deficiency of the enzyme fumarylacetoacetate hydrolase (FAH), which is the last enzyme in the tyrosine catabolic pathway converting fumarylacetoacetate (FAA) into fumarate and acetoacetate. One of the first patients described with TT1 presented with liver cirrhosis, renal tubular defects, and vitamin D-resistant rickets, although the exact diagnosis was not clear at that time [1]. Initially, the primary enzyme defect was considered to be a defect of 4-hydroxyphenylpyruvate dioxygenase (4HPPD) [2, 3]. Some years later, it became apparent that the primary enzyme deficiency was located more downstream in the catabolic pathway of tyrosine at FAH (Fig. 1) [4].

The only existing treatment at that time was dietary restriction of tyrosine and its precursor phenylalanine. Unfortunately, when only treated with a phenylalanine/tyrosine-restricted diet, the outcome was extremely poor. Many TT1 patients did not survive the initial period when presenting with severe liver failure and its associated problems, including ascites and bleeding [5]. If patients survived this period, many died years later due to the development of hepatocellular carcinoma (HCC) or respiratory failure caused by porphyria-like syndrome [5–7]. As a consequence, orthotopic liver transplantation (OLT) was long considered the only definitive option to treat the metabolic as well as the oncological problem [8–10].

This all changed after the introduction of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC, also known as nitisinone) as a new treatment option in 1992 [11]. NTBC proved to be a potent inhibitor of the enzyme 4HPPD, which was first thought to be responsible for the disease. In this way, NTBC can prevent the production of the toxic metabolites FAA, maleylacetoacetate, succinylacetoacetate, and succinylacetone (SA), and thereby substantially improves the clinical outcome [12, 13]. However, as a consequence of 4HPPD inhibition by NTBC treatment, tyrosine concentrations increase substantially further, making a phenylalanine/tyrosine-restricted diet again part of the treatment of TT1 [14].

It is now more than 25 years since NTBC was introduced as a treatment option. Since then, many TT1 patients have been treated with NTBC, most of them in combination with the phenylalanine/tyrosine-restricted diet. Many living TT1 patients are diagnosed after presentation with the associated symptoms, although patients are diagnosed increasingly by population-based newborn screening. This review aims to address the outcome of TT1 patients and long-term considerations in the pharmacological treatment of TT1 patients.

2 NTBC and its Pharmacodynamics and Pharmacokinetics

Naturally occurring triketones are produced by a number of plants and lichens. They are synthesized to prevent growth of surrounding plants [15, 16]. NTBC is such a triketone and was one of the first to be used as a herbicide [17]. Experiments revealed that NTBC is a strong inhibitor of the enzyme 4HPPD [18–20], the second enzyme in the catabolic cascade of tyrosine. 4HPPD catalyzes the conversion of 4-hydroxyphenylpyruvate to homogentisate (Fig. 1). Through NTBC-mediated inhibition of the production of homogentisate, the synthesis of tocopherols and plastoquinones in plants is blocked, thereby reducing the production of chlorophyll. In this way, NTBC causes plants to bleach [18]. In humans, it was postulated that NTBC could block further catabolism of tyrosine into its degradation products [11].

The enzyme 4HPPD is a dioxygenase as its reaction utilizes diatomic oxygen for oxidative decarboxylation as well as aromatic ring hydroxylation [21]. NTBC rapidly and tightly binds to the Fe(II)-containing active site of 4HPPD after a multi-step process. Both NTBC and the substrate 4-hydroxyphenylpyruvate have similar binding interactions, with NTBC especially showing close affinity to the enzyme caused by interactions such as π-stacking. The binding causes a rapid inactivation of the enzyme by creating an almost irreversible 4HPPD inhibitor complex [20, 22–24]. In vitro experiments with tissue of wild-type rats revealed that a concentration of only 100 nM of NTBC was sufficient to block > 90% of the enzyme activity, with only a small amount of activity returning after 7 h [19]. This strong inhibitory reaction was also seen in healthy adult human participants, with a plasma half-life of 54 h after a single dose of NTBC [25].

In rats, NTBC showed a general tissue distribution pattern shortly after dosing, with NTBC detectable in many different tissues including plasma, eye (cornea and glands), liver, kidneys, lung, and a small amount in the brain [26]. However, retention of NTBC was especially apparent in the liver and kidneys of the investigated wild-type rats and mice [26, 27]. NTBC is excreted in urine and feces, each accountable for about 50% of the excretion. In urine, NTBC was excreted unchanged, as 4- or 5-hydroxy metabolites, as amino acid conjugate, or as 2-nitro-4-trifluoromethylbenzoic acid after hydrolytic cleavage, while three unidentified metabolites were detected in rat fecal extracts [28–30].

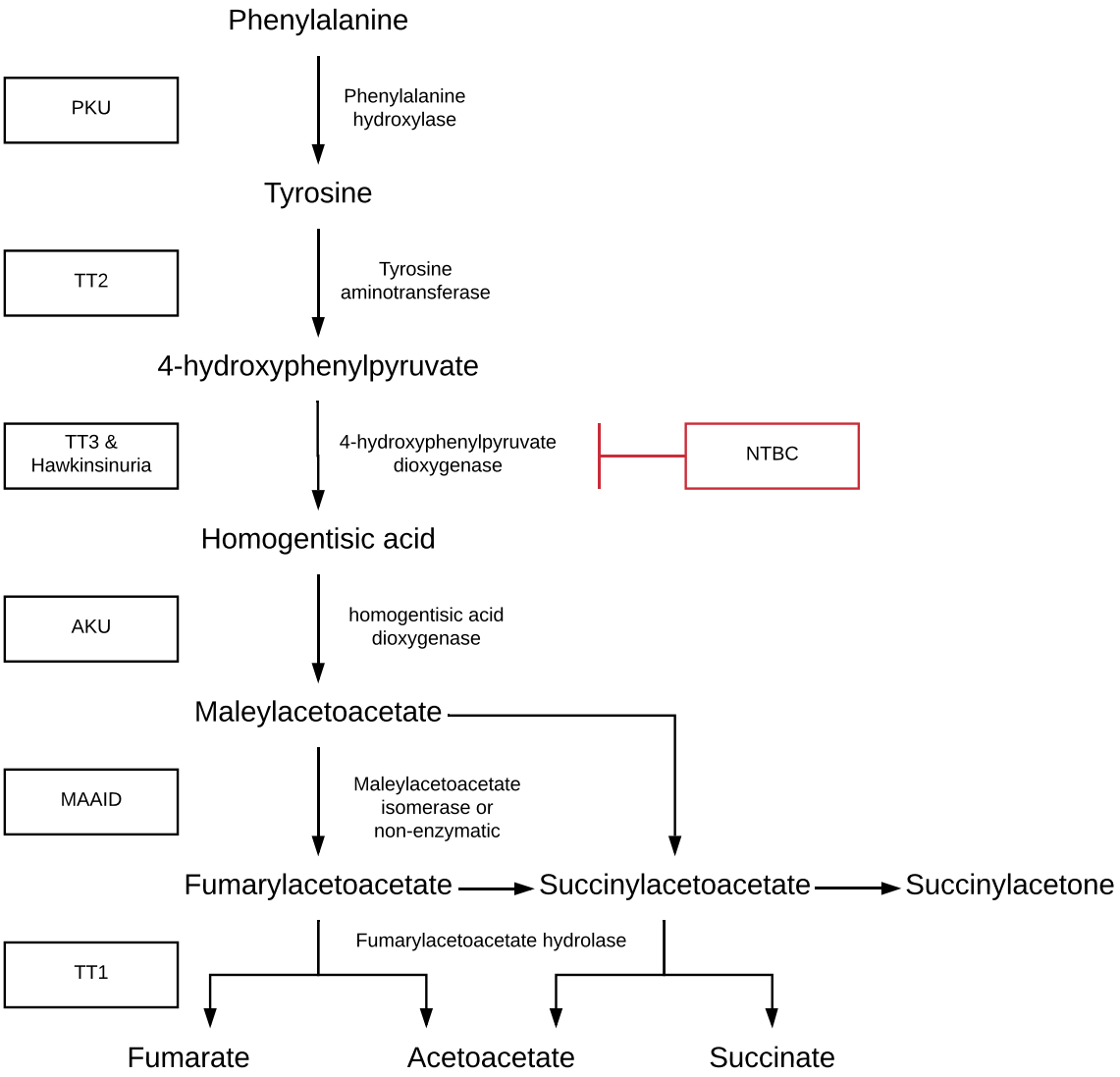

Fig. 1 Phenylalanine and tyrosine degradation pathway is shown with the different enzymes and corresponding associated metabolic disorders, namely phenylketonuria (PKU), tyrosinemia type 2 (TT2), tyrosinemia type 3 (TT3), hawkinsinuria, alkaptonuria (AKU), maleylacetoacetate isomerase deficiency (MAAID), and tyrosinemia type 1 (TT1)

3 Practical Management of NTBC Treatment in Tyrosinemia Type 1 (TT1)

As NTBC inhibits the enzyme 4HPPD, it was considered to be a potential treatment for TT1 patients by creating a metabolic block upstream from the primary enzymatic defect. Lindstedt et al. [11] were the first to treat TT1 patients with NTBC. The first five patients were treated with NTBC 0.1–0.2 mg/kg/day, which was gradually increased to 0.4–0.6 mg/kg/day. Treatment with NTBC led to a tremendous improvement of hallmark biochemical abnormalities, including a decrease in urine and blood SA concentrations, improvement of porphobilinogen synthase activity in erytrocytes and lower urine 5-aminolevulinic acid (5-ALA) concentrations. As a consequence, resulting clinical symptoms such as liver failure and kidney problems improved [11].

Nowadays, the recommendation in Europe, the US, and Canada is to treat patients with 1 mg/kg/day [14, 31–33], although there is some advice to start with 2 mg/kg/day in case of acute liver failure [14], while chronic treatment in stable patients is sometimes given at much lower NTBC doses of around 0.36–0.6 mg/kg/day [34–36]. Some reports state that NTBC once a day is enough as blood concentrations tend to be stable for at least 24 h [14, 25, 37, 38], while others favor giving NTBC twice a day to adequately prevent raised bloodspot SA concentrations [33, 39]. In addition,

the optimal time for blood sampling is not known and may be dependent on the timing of NTBC administration [39].

Dose optimization of NTBC could be done based on several (indirect) parameters, such as (i) doses individually adjusted to mg/kg body weight, (ii) porphobilinogen synthase activity in erythrocytes, (iii) plasma 5-ALA concentrations, (iv) plasma or blood spot NTBC concentrations, or (v) urine, plasma, or blood spot SA concentrations [11, 12]. Unfortunately, recommendations for target blood spot NTBC concentrations are hampered by large inter- and intraindividual variabilities and lack of standardization of NTBC assays [36, 37, 40–44]. Therefore, target blood NTBC concentrations vary mostly between 30 and 60 µmol/L, although concentrations ranging between 20 and 150 µmol/L have been reported [14, 32–34, 40, 45, 46]. A detectable or increased SA concentration in blood spots or plasma, or its excretion in urine, is considered to be a sensitive indicator for suboptimal NTBC treatment and reason for adjustment of therapy [32, 33]. Urine was long considered to be the preferred matrix, mainly because analytical methods were not sensitive enough to analyze the low SA concentrations in plasma or blood spots. However, new techniques have led to a clear improvement in sensitivity [47]. There is currently no consensus on the preferred matrix for monitoring SA. A further increase in the sensitivity of the analytical methods allowed a few laboratories to detect SA in blood spots in healthy individuals, which was previously unnoticed. Therefore, with NTBC treatment, SA concentrations should be targeted to the reference range, but its clinical relevance clearly needs to be established in the coming years [32, 48].

To date, there have been only a few reports about adherence to NTBC. One study reported a high level of adherence to the NTBC medication, with only 1 day of reported nonadherence in a 10-week period [49], while others reported adherence problems in about 15% of the patients [50, 51]. Single cases reported that discontinuation of NTBC for 1–8 weeks resulted in severe, life-threatening neurological crises with diaphragm paralysis and respiratory failure [46, 52–56]. However, it is not known whether the use of NTBC was already suboptimal for a longer period of time in these patients. It could be hypothesized that long-term suboptimal use of NTBC is the most important reason for later development of HCC, as has been reported in TT1 mice [57]. Regular measurement of NTBC and SA in blood spots [36, 39, 40, 42, 47] might increase treatment adherence and therapy adjustment accordingly. Further investigation on optimal treatment regimens and cut-off values for biomarkers are therefore essential.

4 NTBC Treatment in Other Disorders of Tyrosine Metabolism

As NTBC inhibits the enzyme 4HPPD, it could not only be useful in TT1 but in other disorders of tyrosine metabolism caused by an enzymatic defect downstream from 4HPPD as well. Alkaptonuria (AKU), caused by a deficiency of homogentisate dioxygenase, is one of them (Fig. 1). AKU is characterized by high homogentisic acid concentrations that could result in depositions in connective tissue among others, leading to spondyloarthropathy, cardiac valve disease, stone formation, and osteopenia [58, 59]. A total daily dose of only 2 mg NTBC already resulted in 95% reduction of urinary homogentisic acid [60, 61]. Interestingly, this NTBC dose is much lower than the dose given to TT1 patients. This could at least partly be explained as the aim in TT1 is to have no activity of 4HPPD at all, while this is different in AKU. Although this low dose of NTBC initially failed to show a response on non-biochemical outcomes [60], a decrease in clinical progression of eye and ear ochronosis in AKU patients has recently been reported [62, 63]. It is not known whether long-term NTBC treatment in AKU is effective, neither is it known whether NTBC could prevent the severe bone disease caused by ochronosis in AKU patients if started early.

Maleylacetoacetate isomerase deficiency (MAAID) (Fig. 1) has only been found and reported rarely. MAAID is responsible for the conversion of maleylacetoacetate to FAA and is characterized by relatively mildly increased plasma and urine SA concentrations and a normal amino acid profile [64]. The first reported patient with proven MAAID had severe liver and renal failure. However, a favorable outcome without any liver or renal disease has recently been described in six untreated MAAID patients [64]. This is in agreement with the MAAID knockout mice that under normal circumstances did not show a clinical phenotype, although liver and renal damage could be induced by a phenylalanine-enriched diet [65]. Thus, it can't be excluded that MAAID patients under certain circumstances could show liver and renal problems. However, for now there seems no need for NTBC in the regular treatment of MAAID.

Another rarely reported disease of tyrosine metabolism is hawkinsinuria. Hawkinsinuria is not caused by a defect downstream of 4HPPD like the previously mentioned diseases, but is supposed to be caused by an autosomal dominant mutation in the 4HPPD enzyme itself [66–68]. Next to hypertyrosinemia, this mutation causes the formation of hawkinsin instead of homogentisate [68]. It is not certain whether this defect always results in clear clinical manifestations, although transient metabolic acidosis during infancy with vomiting and diarrhea and consequently failure to thrive have been reported [69–73]. In rats, NTBC has shown

to inhibit the mutant 4HPPD enzyme in a similar way as the normal 4HPPD enzyme, indicating a possible treatment strategy for symptomatic infants with hawkinsinuria [68].

Apart from 4HPPD defects or defects downstream of 4HPPD, phenylketonuria (PKU) could also be reasoned to benefit from NTBC treatment [74]. Due to the competitive effect on the blood–brain barrier, high plasma phenylalanine concentrations could, among others, lead to low brain tyrosine concentrations [75]. When increasing plasma tyrosine concentrations by NTBC, it could be reasoned that plasma phenylalanine:tyrosine ratios and consequently brain phenylalanine, tyrosine, and dopamine concentrations improve. This in turn might improve the neurocognitive outcome [76–79]. Data from Harding et al. indeed showed that treatment with NTBC in PKU mice led to a clear decrease in brain phenylalanine and increase in tyrosine and dopamine concentrations and could thus be an adjunct therapy in PKU [74].

5 Adverse Effects of NTBC

NTBC seems to be well tolerated with only a few reported adverse effects. One of the main concerns about the treatment with NTBC are the eye problems associated with it. Most of the rats treated with NTBC soon developed corneal opacities [26]. The similarity between the corneal problems in NTBC-treated rats and rats fed with a tyrosine-enriched diet led to the conclusion that the corneal lesions are caused by the poor solubility of tyrosine and are thus secondary to the increase in tyrosine concentrations induced by NTBC rather than a toxic effect of NTBC itself [26, 80]. However, this could not be the only explanation as clear interspecies differences in ocular problems are found [27, 28, 81].

Due to the associated increase in tyrosine concentrations and secondary development of ocular problems, NTBC treatment has from the start been combined with a phenylalanine/tyrosine-restricted diet [11]. Currently, treatment recommendations vary between different centers and countries, with upper tyrosine concentrations varying between 400 and 600 μmol/L [14, 31–33, 82, 83], although higher levels up to 800 μmol/L are sometimes accepted in practice [45]. Despite the dietary restriction, eye problems are still found in approximately 5–10% of the TT1 patients [12, 31]. The most frequently reported eye problems are transient itching, burning, and photophobia [12, 31, 51], although silent keratopathy, clinical corneal opacities, or even corneal crystals presenting as pseudodendritic lesions have been reported [12, 46, 63, 84–87]. Although no clear correlation between ocular problems and tyrosine concentrations could be found, withdrawal of NTBC or stricter adherence to the phenylalanine/tyrosine-restricted diet resolves the corneal lesions [12, 13, 87]. Therefore, ophthalmic follow-up is necessary and in case of eye problems, specific eye investigations with a slit lamp should be considered, while the diet should be intensified [82, 88].

In addition to high tyrosine concentrations caused by NTBC treatment, phenylalanine concentrations below the lower limit of normal are often found in TT1 patients [11, 13, 89–92]. Although these low phenylalanine concentrations are usually expected to be caused by the phenylalanine/tyrosine-restricted diet, NTBC itself seems to lower plasma phenylalanine concentrations as well [74]. The mechanism by which NTBC treatment lowers plasma phenylalanine is not understood. Low phenylalanine concentrations have been associated with growth retardation, neurological impairments, and skin problems in an infant with TT1 [91]. Therefore, phenylalanine supplementation has been suggested to prevent these low phenylalanine concentrations, although the exact dosage and its effect on phenylalanine concentrations is not clear yet [33, 89, 91, 93]. No uniform consensus guidelines exist, but the usual advice is to keep phenylalanine concentrations within the normal range (38–78 μmol/L) [32, 94]. Because of the expected drop in phenylalanine concentrations in the afternoon, we advised to keep fasting phenylalanine concentrations above 50 μmol/L [92].

Other reported adverse effects of NTBC are relatively uncommon, minor, and/or transient and usually do not require disruption of NTBC treatment. The most frequently reported adverse effects (except for ocular problems) are leukopenia, thrombocytopenia, or granulocytopenia (all < 10%), and pruritus, exfoliative dermatitis, erythematous rash, myoclonia, or constipation (all < 1%) [12, 14, 45, 46, 50, 63, 95].

6 Outcome in TT1 Before and After Introduction of NTBC

6.1 Liver Problems

Especially FAA, but maybe also maleylacetoacetate, has been shown to be cytotoxic and mutagenic and causes glutathione depletion, oxidative stress, chromosomal instability, cell cycle arrest, and apoptosis in the cells where it is generated, primarily hepatocytes [96–99]. As a consequence, TT1 is characterized by progressive liver disease, and could be classified into different categories based on their moment of presentation, associated symptomatology, and resulting outcome [5]. The majority of the patients presented (very) early with severe acute liver failure and associated pronounced coagulopathy, ascites (with or without spontaneous bacterial peritonitis) due to low albumin concentrations, and hypoglycemia. In particular, these early presenting patients had a poor outcome, with only 10–30% of the patients still alive 2 years after diagnosis [5, 100]. In later presenting patients, liver problems are usually less pronounced, although HCC

could be present already [5, 101–105]. When patients survived the initial period, there was a high risk for developing chronic liver disease, cirrhosis, and eventually HCC when treated with a phenylalanine/tyrosine-restricted diet only [5, 6, 104]. Therefore, OLT was long considered the only definitive option to prevent metabolic and oncological problems [8–10, 103, 106–110].

The introduction of NTBC results in a quick recovery of liver function, although about 10% of the patients with (acute) liver failure do not respond to the treatment [12, 31, 50, 83, 111]. In most patients, the coagulopathy quickly resolves, porphobilinogen synthase activity reaches normal levels within a month, 5-ALA excretion in urine normalizes in most cases, and urinary and blood SA concentrations normalize completely after some days or months, respectively [11, 31, 83, 112]. Alfa-fetoprotein (AFP), the biochemical marker for HCC in TT1, decreased slowly over some months to normal values. The risk of liver cancer (mainly HCC, although hepatoblastoma could occur) decreased tremendously and is estimated to be around 1% if NTBC treatment is initiated early [11, 13, 31, 83, 113]. In line with this, long-term follow-up revealed that NTBC-treated TT1 patients are still at risk for HCC, especially when NTBC is initiated late due to delayed diagnosis or unavailability of NTBC [13, 31, 46, 55, 114–121].

So far, no HCC development in pre-clinically treated patients has been reported [13, 120, 122–124]. However, HCC is still seen in TT1 mice, even if NTBC is started prenatally and high amounts are given after birth in combination with a phenylalanine/tyrosine-restricted diet [125, 126]. In addition, gene expression patterns and collagen metabolism are also not fully normalized in TT1 patients receiving NTBC [127, 128]. Due to this increased risk to develop HCC, screening is still recommended using regular AFP measurements and imaging such as ultrasound and magnetic resonance imaging (MRI) in case of a suspect lesion [14, 32, 45, 82, 123, 124]. In contrast to other diseases with a high risk of developing HCC (e.g., hepatitis B and C), AFP has always been considered a reliable marker for liver cancer in TT1 [14, 113, 115]. However, HCC may develop without clear rise in AFP and additional markers are currently being investigated [118, 124, 129]. Thus, at present, both a lesion at imaging and a rise in AFP should be considered pathognomonic for HCC, while a slow decrease of AFP, or an AFP level that remains above the upper limit of normal after 2 years of age are predictive signs of HCC development and should be discussed with the OLT team as well [115, 118].

6.2 Renal Problems

FAA not only affects hepatocytes, but tubular cells of the kidney as well. FAA can cause oxidative stress, acute apoptosis, and cellular death in proximal tubular cells just as in hepatocytes [130]. In addition, SA has been shown to reduce sugar and amino acid uptake in the proximal tubulus leading to renal Fanconi syndrome [130, 131]. In contrast to liver failure, these renal tubular problems are apparent as well in late-presenting TT1 patients [45]. The characteristic renal disease in TT1 patients is a renal tubulopathy with aminoaciduria, glucosuria, phosphaturia, and acidosis (that is difficult to fully correct) and, as a consequence, secondary hypophosphatemic (vitamin D-resistant) rickets may develop. However, the severity of the renal problems varies significantly between patients [45, 50, 55, 132]. Dietary restriction of phenylalanine and tyrosine and supplementation of minerals and vitamins seem to improve renal tubular defects (even without NTBC) in some patients. In dietary-treated patients, this partial response together with non-adherence may result in progression to nephromegaly, nephrocalcinosis, glomerulosclerosis, or even renal failure [133–138].

Administration of NTBC in patients with renal tubular dysfunction results in an improvement in kidney function with normalization of phosphate reabsorption and plasma phosphate concentrations, usually within a month [11, 136, 139], although sometimes less rapidly than for the liver problems. A slower but continuous improvement could be seen in other parameters such as glucosuria, proteinuria, excretion of macroglobulin, plasma uric acid, plasma calcium, and rickets within the following years; mineral and vitamin supplements could usually be withdrawn [111, 132, 136, 139, 140]. Long-term follow-up of adequately NTBC-treated patients revealed a normal tubular function in most of the patients [34, 132, 138], although minor tubulopathy without clinical consequences and already existing nephrocalcinosis may persist [46, 50, 51, 132, 136]. In pre-clinically diagnosed patients, none of the patients showed clinically significant renal problems at diagnosis or developed renal problems while on NTBC [13, 122]. Annual clinical follow-up with laboratory evaluation and renal ultrasound is recommended for TT1 patients [32, 45].

6.3 Neurological Problems

Recurrent neurological crises could be present in up to 40% of the TT1 patients treated by diet alone and were a main cause of hospitalization or even mortality [5, 7]. The neurological crises were usually provoked by a minor infection and presented as a peripheral neuropathy with hypertonia, paralytic ileus with vomiting, or muscle weakness that could progress to paralysis or even respiratory failure that could mimic the progressive weakness in Guillain–Barre syndrome [7, 141].

Treatment with NTBC results in a rapid decline in SA, resulting in an increase in porphobilinogen synthase activity

and, as a consequence, normalization of 5-ALA concentrations that were thought to be responsible for the neurological crises or so-called porphyria-like-syndrome [7, 11]. As a result, the neurological symptoms have completely disappeared after the start of NTBC treatment [13, 31, 50, 141]. However, when NTBC treatment is interrupted, severe neurological crises may reappear, mimicking the porphyria-like-syndrome described above.

6.4 Neuropsychological Problems

No consistent cognitive or behavioral deficiencies were reported in TT1 patients prior to the introduction of NTBC. In contrast, intellectual development and school performance was considered to be normal, even in patients with recurrent neurological crises. However, in more recent years, after the introduction of NTBC, several studies reported a non-optimal cognitive development in TT1 patients. In 2008, 35% of French TT1 patients retrospectively showed school problems [50]. Later research showed a broad range of neurocognitive problems, especially in children with TT1. These neurocognitive problems include a lower (performance and verbal) IQ [46, 119, 142–144] and even regression of IQ over time [145, 146], abnormal motor skills [143, 147], impaired executive functioning (including affected working memory and cognitive flexibility), and non-optimal social cognition [144, 147] and behavioral problems such as attention deficits [148]. Next to these neurocognitive problems, structural changes in the brain are found in some TT1 patients. MRI of two TT1 patients showed white matter problems and myelination deficits [149, 150] and positron emission tomography/computed tomography scans showed abnormal bilateral hypometabolism in one out of three adult patients [147]. However, this is contradicted by the study of Thimm et al. that showed no MRI abnormalities [143]. Various hypotheses have been suggested to explain these neurocognitive disturbances: (i) the disease itself, with toxic products and associated liver failure [151, 152], (ii) treatment with NTBC, (iii) high plasma tyrosine concentrations either being toxic in itself or changing neurotransmitter metabolism, (iv) high plasma tyrosine concentrations that compete with the uptake of other amino acids and thus impair cerebral protein synthesis in general or impair neurotransmitter synthesis caused by decreased brain influx of tryptophan, or (v) low plasma and corresponding brain phenylalanine concentrations [141]. To test these different hypotheses, associations between the neurocognitive deficiencies and alterations of blood TT1 phenylalanine or tyrosine concentrations have been sought. So far, no specific group of TT1 patients at risk for neurocognitive deficiencies could be identified, as non-optimal neurocognitive outcomes have been seen in pre-clinically diagnosed, clinically diagnosed, and transplanted patients [144, 153]. Also, a correlation between low blood phenylalanine or low phenylalanine/tyrosine ratio and neurocognitive outcome was found only in two studies [142, 146]. To investigate this further, Thimm et al. measured increased tyrosine concentrations in cerebral spinal fluid while 5-HIAA concentrations were decreased, possibly indicating central nervous system serotonin deficiency, but no direct measurement of brain serotonin has been made in TT1 [154].

During clinical follow-up, psychomotor and intelligence testing is rarely routinely performed [45], although it has been advised to perform neuropsychological testing before school age and at regular intervals afterwards [14, 32].

6.5 Other Symptoms

Hypertrophic obstructive cardiomyopathy has been a rarely reported symptom in TT1 patients treated with a phenylalanine/tyrosine-restricted diet [104, 155, 156], which reportedly resolves completely within some months after start of NTBC treatment [157–159]. Other rare reported accompanying symptoms at diagnosis include transient carnitine deficient myopathy, likely caused by renal Fanconi tubulopathy [160], and transient hyperinsulinism with hypertrophy of the islets of Langerhans [100, 161]. To date, there have been no reports of adverse cardiac symptoms while taking NTBC [158], nor about any other of the rarely reported complications mentioned above.

7 Future Considerations and Remaining Challenges for TT1

7.1 Pregnancy

With the tremendously improved clinical outcome and survival probability, pregnancy in TT1-affected mothers treated with NTBC have been reported [162–164]. Not much is known about a possible teratogenic effect of NTBC. However, very high dosages of NTBC have been associated with corneal lesions, malformations, and reduced survival in offspring of NTBC-treated laboratory animals [162], while prenatally prescribed normal dosages do prevent early death in TT1 mice and pigs without any teratogenicity [57, 165].

In human pregnancies, NTBC has been continued in all three reported cases. Two unaffected children had a normal birth weight, while the birth weight of one child with TT1 was in the low normal range. All three infants were healthy without signs of malformations and had normal development later on while receiving between 0.5 and 1.0 mg/kg NTBC during pregnancy with maternal tyrosine concentrations up to 700–800 μmol/L [162–164]. After delivery, neonatal blood NTBC concentrations reduced slowly while receiving bottle feeding [163, 164], until SA became detectable in urine and AFP concentrations rose slightly after an

initial decline 2 weeks after birth in the TT1-affected child [162]. All reported TT1 mothers were healthy with no sign of liver, renal or neurological deterioration during pregnancy [162–164].

Although no clear guidelines exist and existing data is limited, current knowledge suggests that NTBC treatment in pregnant TT1 patients should be continued with strict monitoring considering the possible complications for the pregnant TT1 patient associated with an interruption in NTBC treatment [48].

7.2 Long-Term Follow-Up

With the introduction of NTBC, the outcome of TT1 patients improved considerably as explained above. As about 10% of the patients presenting with liver failure do not respond early enough to NTBC to prevent OLT, and the risk of HCC is still clearly elevated when NTBC treatment is started late, a further improvement reduction in liver-related morbidity is expected with the universal introduction of neonatal screening [13, 122]. With early introduction of NTBC, important clinical symptomatology can be prevented, although the very long-term effects of NTBC, both in terms of effectiveness and toxicity, remain to be evaluated. At this time, it is clear that strict follow-up for possible HCC is still needed as it is not certain whether NTBC only delays the development of HCC or completely prevents HCC formation when started after pre-clinical neonatal diagnosis. However, in light of the uncertain long-term effectiveness and potential new toxicities, strict monitoring of the disease is of crucial importance. This is hampered by the fact that no clear guidelines on effective dosing and safe concentrations of NTBC and safe concentrations of biochemical parameters such as blood or urine SA, and blood tyrosine and phenylalanine concentrations currently exist. Therefore, neurocognitive, psychosocial, ophthalmic, physical, and nutritional follow-up is necessary to prevent complications of high tyrosine concentrations and to assess vitamin and mineral status. Furthermore, continued research is necessary to address the neurocognitive functioning, its relationship with current treatment strategies, and to reveal the pathophysiological mechanisms causing the brain impairments.

7.3 Considerations from a Cost Perspective

NTBC is one of the 20 most expensive drugs [166], with reported annual costs between US $70,000 and US $140,000 for a person of 50 kg depending on manufacturer and country of issue [167, 168]. Despite this, only one cost-effectiveness study has been performed [169]. As a consequence of the improved clinical outcome, NTBC lowered the utilization of health care and associated costs for hospital visits and admissions, although total yearly costs increased significantly with NTBC treatment [169].

Developing drugs for rare diseases, the so-called orphan drugs (affecting < 1:2000 individuals according to criteria in the EU) has been—and still is—an unmet need in many of those rare and ultra-rare diseases. However, with the adoption of Regulation (EC) No. 141/2000 in the EU, many new orphan drugs are coming to market every year as a result of intensifying rare disease research and drug development. Incentives for companies, including fee reductions and, importantly, 10-year market exclusivity, has stimulated this development. In combination with an emphasis on personalized medicine as a consequence of advances in (genetic) technology, the drug market is switching towards development of orphan medicines.

Although patients, families, and healthcare professionals welcome more treatment options, this increasing 'orphanization' of the healthcare system has fueled concerns among regulatory bodies, payers, healthcare professionals, and patients because of the high prices. A major concern in this respect is the observation that some orphan medicines reach the market in an immature stage: while pivotal trials show promising results, insufficient knowledge of long-term, clinically relevant outcomes and the price in itself withholds reimbursement, which leads to unequal access to orphan drugs [170]. Hence, new pharmaceutical developmental models need to be developed, including better and more independent evaluation of outcomes, for example in adaptive pathway models [171] as well as reimbursement models, taking cost effectiveness, uncertainty, and development costs into consideration. With regard to NTBC, all of the above applies; uncertainty of long-term effectiveness and toxicity requires improved, collaborative monitoring, with open data sharing and independent outcome analysis. This is important to support healthcare professionals to make rational choices for treatment for the benefit of their patients: at this time, partly because of costs, some centers advocated to perform OLT instead of the conservative treatment with NTBC and a combined phenylalanine/tyrosine-restricted diet.

7.4 Possible New Strategies

So far, no HCC has been reported in pre-clinically diagnosed TT1 patients. However, as FAH is expressed in utero and AFP concentrations are raised at birth, a prenatal start to liver disease is likely [57, 172, 173]. Therefore, prenatal diagnosis and prevention of prenatal liver disease could theoretically be achieved with the prescription of NTBC to unaffected mothers. Alternatively, recent advances have shown in utero gene editing to abolish neonatal lethal liver disease in TT1 mice [174]. As TT1 mice still develop HCC even if 90–95% of the liver cells are corrected, long-term efficacy of cell or gene therapy was thought to require all

liver cells to be targeted to prevent HCC formation in original FAH deficient cells [125, 175]. However, liver-directed gene therapy in a TT1 pig has been shown to be effective without signs of liver fibrosis or HCC development after 3 years of follow-up and could thus be a potential alternative therapeutic approach that needs to be explored [176].

8 Conclusion

This review showed that NTBC has clearly improved the treatment and outcomes for patients with TT1. During the last 25 years, NTBC treatment has proved to be generally safe, well tolerated, and effective. Where OLT was once considered the only definitive option, OLT is now only used in cases that fail to respond to NTBC and when liver cancer develops. To further reduce the risk of long-term complications such as HCC and neurocognitive issues, and to prevent clinical symptoms, pre-clinical diagnosis with blood spot SA measurements in newborn screening is necessary. The exact risks for the development of complications associated with the disease, NTBC, and long-term dietary treatment are not known yet and therefore strict follow-up is necessary. Future challenges will be to develop uniform guidelines for treatment and follow-up, reliable detection of possible liver cancer, and weighing the risks, challenges, and costs of existing and alternative strategies for the treatment of TT1.

Compliance with ethical standards

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Conflict of interest ILR has received research grants from SOBI. CEMH is involved in pre-marketing studies with Sanofi, Protalix, and Idorsia in the field of lysosomal storage disorders. She is advisor for drug regulatory agencies and a member of the Advisory Committee to the insurance package of the National Heath Care Institute. FJvS has received research grants, advisory board fees, and speakers honoraria from Nutricia Research, Merck-Serono, Biomarin, Codexis, Alexion, Vitaflo, MendeliKABS, Promethera, SOBI, APR, ARLA Foods Int., Eurocept, Lucane, nestle-Codexis Alliance, Orphan Europe, Rivium Medical BV, Origin, Agios, NPKUA, ESPKU, NPKUV, Tyrosinemia Foundation and Pluvia Biotech. WGvG, COH and MRHF have indicated that they have no potential conflicts of interest to disclose.

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