Treatment of Galactosemia

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Galactosemia is an inborn disorder of carbohydrate metabolism characterized by the inability to metabolize galactose, a sugar contained in milk (the main source of nourishment for infants), and convert it into glucose, the sugar used by the body as the primary source of energy. Galactosemia is an autosomal recessive genetic disease that can be diagnosed at birth, even in the absence of symptoms, with newborn screening by assessing the level of galactose and the GALT enzyme activity, as GALT defect constitutes the most frequent cause of galactosemia. Currently, galactosemia cannot be cured, but only treated by means of a diet with a reduced content of galactose and lactose. Although the diet is able to reverse the neonatal clinical picture, it does not prevent the development of long-term complications.

galactosemia | newborn screening | galactose metabolism | classical galactosemia | gene-based therapies | small molecules therapies

1. Introduction

Diet is the cornerstone of the treatment of CG, GALK1 deficiency, and generalized GALE deficiency aiming at minimizing galactose intake [1][2]. Individuals with intermediate GALE deficiency should receive a galactose-restricted diet at least in infancy [2]. With only 10 patients with GALM deficiency having been reported, the need for galactose restricted diet is currently assessed on a case-by-case basis [3][4]. A galactose-restricted diet (e.g., discontinuation of breast milk or whey-based infant formula) is effective in preventing or resolving acute neonatal life-threatening symptoms (e.g., vomiting, poor feeding, lethargy, metabolic acidosis, jaundice, abnormal clotting, liver failure) [5]. A more favorable outcome has been observed in patients starting a galactose-restricted diet in the first week of life [6]. Soy-based formulas or elemental formulas are employed as the only feeding source before weaning [7]. Although casein protein hydrolysate formula contains traces of lactose, it is also considered safe in CG [5]. Recommendations on (the introduction of) complimentary food have changed over time. In the 1990s, the evidence of the presence of free galactose in a wide variety of foods resulted in highly restrictive indications [8]. More recently, a less restricted diet has not been associated with an increased risk of neurological complications [6]. Currently, animal milk and dairy products are restricted [9], while there is no evidence that the consumption of food containing trace amounts of galactose (e.g., fruit, vegetables, and legumes) has any adverse effects on patients' outcomes [7]. Mature cheeses and soy-based products are allowed based on their relatively low galactose content (<25 mg/100 g) as compared to endogenous galactose production (>24.8 mg/kg/day in newborns, 8.4 mg/kg/day in adults) [10][11]. Conversely, there is still limited evidence to support specific age-related

recommendations for the amount of galactose allowed in the diet [5]. As dietary restriction may result in calcium and vitamin D deficiency, both should be supplemented as necessary.

Since children with Duarte galactosemia do not present with clinical symptoms but are detected via NBS, there is an ongoing debate about whether dietary treatment is needed. The most common practice is not to treat individuals with Duarte galactosemia [5]. Yet, some metabolic centers prescribe a galactose-restricted diet in the first year of life [12] usually followed by a galactose challenge around age one year [13].

Irrespective of the dietary treatment approach, patients with CG are still at risk of developing long-term complications, such as intellectual disability, primary ovarian failure, and reduced bone mineral density [6]. This suggests that the development of long-term complications may depend on the combination of individual exogenous galactose tolerance (as reflected by the genotype) and other factors, such as impaired protein glycosylation, epigenetic regulation, and activation of inflammatory pathways [14]. In order to develop novel treatments able to prevent long-term complications, various options are currently being investigated in preclinical and/or clinical studies (see **Table 1** for ongoing clinical trials). Therapeutic compounds can be classified into two main groups: (1) gene-based therapies and (2) small molecules.

Table 1. Ongoing interventional clinical trials for novel treatments in galactosemias.

Condition	Drug	Approach	Participant Age	Study Phase	Study Identifier
CG	AT-007	Enzyme inhibitor	2–18	2/3	NCT04902781
CG	AT-007	Enzyme inhibitor	18–55	1/2	NCT04117711
CG	BBC	Behavioral	0.2–4.5	N.A.	NCT03838016
CG	N.A.	Cryopreservation	4–12	N.A.	NCT04948658

Data retrieved from Clinicaltrials.gov, last accessed on 23 May 2022. BBC: babble boot camp; CG: classic galactosemia; N.A.: not applicable.

2. Gene-Based Therapies

Gene-based therapies include gene therapy and mRNA therapy and aim at restoring GALT activity up to 10–15%, thus preventing clinical disease [1]. *GALT* gene therapy with various adeno-associated virus (AAV) vectors resulted in increased GALT levels in the liver (64–595%) and brain (3–42%) in GALT null rat pups without significant adverse effects. A reduction in galactose, galactitol, and galactose 1-P concentrations in the liver, blood, and brain as well as an improvement in cataracts were also observed [15]. Biochemical and clinical improvement was observed up to 2 months in treated rats, suggesting efficacy of gene replacement through early adulthood [16]. Restored GALT activity and protein level as well as reduced oxidative stress were also observed in fibroblasts of CG patients transduced with AAV2-CMG-hGALT [17]. Despite its potential benefit, the observed difference between liver and brain GALT activity as well as the immune response to AAV vector and genomic instability warrant further studies before gene therapy can translate into clinical practice [18].

Like other inborn metabolic disorders, the effect of mRNA therapy has also been investigated in CG. mRNA can be encapsulated in various vehicles (e.g., liposomes, nanoparticles, viruses) and delivered to the site of action where it is translated into a functional protein [19]. A single GALT mRNA dose soon after birth reduced mortality in GALT-deficient mice fed a milk diet. Additionally, a dose-dependent increase in GALT expression and activity in the liver as well as decreased galactose 1-P levels in the liver, red blood cells, and peripheral tissues were observed in GALT-deficient mice treated with GALT mRNA using lipid nanoparticles (LNP) [20]. Consistently, administration of LNP-packaged hGALT mRNA was safe and restored GALT protein levels and activity in a zebrafish model of CG [21]. Tailoring LNP to target extrahepatic tissues (e.g., brain, gonads), defining the most effective dosing interval, and assessing the mRNA-induced immune response remain important challenges to developing mRNA therapy as a treatment for CG.

3. Small Molecules

Small molecules under investigation for the treatment of CG include: (1) pharmacological chaperones, (2) enzyme inhibitors, and (3) endoplasmic reticulum (ER) stress-reducing agents.

Pharmacological chaperones are low molecular weight compounds that bind specifically to their target (protein) and stabilize it [22]. As such, they can facilitate protein folding and intracellular trafficking and/or prevent premature degradation [23]. Although pharmacological chaperones present several advantages (e.g., oral availability, potential to cross the blood–brain barrier), they cannot be used in all patients. While being effective in rescuing missense variants beyond the active site, they are not useful in case of deletion, stop gain variants, splicing variants, or active site variants [23]. Thanks to its anti-aggregation property, arginine has been studied as a potential treatment option for CG. Although initial studies suggested a potential benefit of arginine on specific GALT variants [24], subsequent research failed to confirm an effect of arginine on GALT stability [25]. As at least two binding sites (i.e., active site and binding site for allosteric modulators) in the GALT exist [24], a combination of in silico screening of predicted ligands, screening of chemical libraries, and rational screening of substrate is expected to identify novel drug candidates in the future. Yet, definition of the safety profile, appropriate (age-dependent) dosing, and specific indications (i.e., GALT variants) remain major challenges [26].

Enzyme inhibitors include galactokinase 1 (GALK1) inhibitors and aldose reductase (AR) inhibitors.

GALK1 inhibitors aim at reducing galactose 1-P accumulation, which plays a key role in the pathogenesis of CG [27]. Several candidate compounds have been identified by high-throughput screening. Among these, phenylsulfunamides have been shown to lower galactose 1-P levels in fibroblasts from CG patients [28]. More recently, non-competitive GALK1 inhibitors have been identified with the potential for further development in clinical trials [29]. As the in vivo effect of such inhibitors remains to be elucidated, additional research beyond cellular models is warranted.

AR inhibitors target galactose conversion to galactitol, which accumulates in cells leading to cell swelling and apoptosis in CG [30]. Particularly, accumulation of galactitol within the lens causes galactosemic cataracts [31].

Galactitol accumulation may also play a role in the development of neurological symptoms [30]. Originally developed for the treatment of diabetes [32], AR inhibitors decreased galactitol levels in plasma, liver, and brain and prevented cataract formation in GALT-null rat models [30][33]. Attenuation of galactitol-induced Schwann cell injury has also been observed in galactosemic rats treated with an AR inhibitor [34]. Whether AR inhibitors are able to address extraocular symptoms (e.g., cognitive symptoms, subfertility) remains to be established. Moreover, the potential effect of blocking the galactose conversion to galactitol (e.g., galactonate increase) remains to be elucidated [35].

ER stress has been demonstrated in fibroblasts from both GALT-null mice [36] and galactosemic patients [37]. Particularly, downregulation of the PI3K/Akt pathway may play a role in subfertility and ataxia [36]. Salubrinal is a eukaryotic initiation factor 2α (eIF2α) inhibitor that upregulates the cellular stress response, thus alleviating ER stress [38]. Reduced loss of both Purkinje cells in the cerebella and primordial ovarian follicles without detectable adverse effects was observed in GALT-null mice treated with Salubrinal [39]. Thus, ER constitutes a promising novel therapeutic target to be explored in CG.

4. Other Therapies

In addition to therapies (aiming at) targeting the enzyme defect, approaches addressing the clinical consequences of CG have also been developed. Indeed, despite a galactose-restricted diet, patients are still at risk of developing long-term complications.

Intellectual disability, speech delay, movement disorders, and emotional disturbance are common in CG [6]. Besides current approaches used to treat patients who develop such complications [5], transcranial alternating current stimulation (tACS), and Babble Boot Camp (BBC) are being investigated in CG [30], tACS is a form of non-invasive brain stimulation inducing long-term synaptic plasticity. This approach has proven effective in Parkinson's disease [40] and dyslexia [41]. BBC is a preventive speech intervention program constating active parental involvement guided by a speech specialist. A trend between speech outcomes has been observed in four children with CG receiving BBC as compared to one child with CG who did not receive BBC, supporting the potential benefit of this approach [42].

Hypogonadotropic hypogonadism and primary ovarian insufficiency are common features in female patients with CG [5]. Although pregnancies in women with CG can occur [43], the chances of pregnancy are reduced [5]. Currently, two treatment options to address subfertility can be offered to patients with CG: cryopreservation and oocyte donation. Fertility preservation is only likely to be successful in very young prepubertal patients. Three fertility preservation procedures are available: ovarian tissue, mature oocyte, and/or embryo cryopreservation [44]. Even though cryopreservation reduces the ovarian reserve, this technique is now associated with an increasing success rate and low complication rate [45]. Intrafamilial oocyte donation is another approach to address subfertility in CG. Yet, several topics need to be discussed when considering this option, including the patient's cognitive level, family

relations, and medical impact [46]. As fertility preservation techniques often raise ethical questions, they should only be offered after appropriate institutional research ethics approval [44].

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