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Letter to Editor

Arginase 1 Deficiency: An Ultrarare Urea Cycle Disorder in Childhood

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Letter to The Editor

Arginase-1 deficiency is a rare, autosomal recessive inherited metabolic disorder in which the enzyme arginase-1 is missing or defective by mutation [1-13]. The incidence is very low and is estimated to be about 1:800,000 to 1:1,000,000 [13]. This leads to an accumulation of arginine in the blood, causing untreated progressive spastic paraparesis, developmental delays, seizures, uveoretinitis and cognitive impairments [14-18]. Since 2024, a causal enzyme replacement therapy named Pegzilarginase (Loargys) has been available, which lowers the arginine levels. The disease usually occurs in childhood [1,2,3-6,19-23]. Typical signs include neurological problems with spasticity of the legs, gait disturbances, arthritis and slowed motor development [45]. Cognitive impairments include developmental delays and seizures. Other symptoms include growth delays, eating disorders and smaller head circumference. The disease is progressive, and if left untreated, it can lead to loss of walking ability and severe disabilities [7]. A case report describes a patient with Arginase 1 deficiency undergoing liver transplantation, another a correlation with hepatocellular carcinoma [24,25]. Overexpression of Arginase 1 linked to DMTAA and TET2 mutations in lower grade myelodysplastic syndromes and CML [26].

The urea cycle, also known as the ornithine or Krebs-Henseleit cycle, discovered in 1932 at the University Hospital Freiburg by Hans Adolf Krebs and Kurt Henseleit, is a biochemical cascade in mammals that converts nitrogen-containing breakdown products, especially ammonium, into urea, which is then excreted through the kidneys [27,28,29]. In birds and land-dwelling reptiles, uric acid is produced and excreted instead. Fish do not require the conversion of ammonia, as their skin, in direct contact with water, provides the simple route of osmosis. Urea formation occurs in liver cells (hepatocytes) and to a lesser extent in the kidney. The cycle is partially located in the mitochondria and partially in the cytosol, requiring transport proteins [30]. Partial reactions of CPS-I (catalyzed by carbamoylphosphate synthetase I) show that bicarbonates are phosphorylated and activated, as 1st ATP-dependent reaction. Ammonia is added with the release of the phosphate group, forming carbamate. Carbamate is phosphorylated and activated again, as the 2nd ATP-dependent reaction. The end product is carbamoylphosphate, which is the entry product into the actual urea cycle in the cytosol. Both steps are catalyzed by carbamoylphosphate synthetase I. Since there is no carrier for transporting carbamoylphosphate out of the mitochondria, an initial detour through ornithine-citrulline must occur. Both are non-proteinogenic alpha-L-amino acids, differing only in the carbamate group, and carriers exist for them. Carbamoylphosphate is converted to ornithine by dephosphorylation, resulting in citrulline. This reaction is catalyzed by ornithine transcarbamylase. Citrulline is transported to the cytosol via the mitochondrial ornithine transporters 1 and 2 in an antiport exchange with ornithine. Citrulline is converted to argininosuccinate in the cytosol by adding L-aspartate in an ATP-dependent manner, catalyzed by the enzyme argininosuccinate synthase. Subsequently, argininosuccinate is converted to arginine by argininosuccinate lyase with the release of fumarate. In the final step, the enzyme arginase 1 (ARG1) catalyzes the conversion of arginine to ornithine, consuming

H2O. The resulting isoharnstoff is in equilibrium with urea. The aspartate cycle is used to recover aspartate from fumarate. The reactions are similar to those of the citric acid cycle. Fumarate is converted to malate by the cytosolic enzymes fumarase and malate dehydrogenase, and then to oxaloacetate. During the oxidation of malate to oxaloacetate, NAD is reduced to NADH. Oxaloacetate is transaminated with an α-amino acid to L-aspartate. Glutamic acid is usually used as the α-amino acid, which is deaminated to the α-keto acid α-ketoglutarate during transamination. The catalyzing enzyme is aspartate aminotransferase. Oxaloacetate can also be channeled into gluconeogenesis or transported anaplerotically into the citric acid cycle in the mitochondria via transporters. Malate obtained from fumarate by cytosolic fumarase can also be transported back to the mitochondria via the malate-aspartate shuttle.

Dietary measures for Arginase-1 deficiency aim to minimize the intake of the amino acid arginine to prevent the formation of ammonia and lower blood arginine levels. Since arginase is the enzyme that breaks down arginine, a deficiency leads to toxic accumulation, primarily manifesting as neurological symptoms such as spasticity and developmental delays. Key dietary measures are strict protein restriction. Natural protein must be severely limited to minimize arginine intake. Low-arginine diet by restriction of arginine-rich foods (e.g., nuts, chocolate, legumes, meat, eggs, dairy) is of upmost importance. Supplementation with essential amino acids is necessary. Since the diet is low in protein, a special arginine-free amino acid mixture is necessary to meet the need for essential amino acids and enable normal growth. High intake of carbohydrates and fats is important. To meet energy needs and prevent catabolic states, with protein breakdown in the body releasing arginine, a high intake of non-protein calories, 45-65% of total calories, is required. Nitrogen binders, also known as scavenger drugs, are helpful in addition to the diet, medications like sodium phenylbutyrate are often used to eliminate excess nitrogen through other pathways [31]. A close monitoring of plasma concentrations of arginine and ammonia by a metabolic specialist is essential. No complete avoidance of protein is necessary. Not all protein should be eliminated as the body requires a certain amount for growth and development. As emergency regimen during acute infections, often accompanied by vomiting or fever, protein intake must be immediately stopped, and a specific emergency regimen initiated to prevent metabolic decompensation. The diet should always be supervised by a specialized metabolic team and dietitians.

Pegzilarginase (Loargys) consists of a cobalt-substituted, recombinant human arginase-1 enzyme produced in Escherichia coli cells and covalently conjugated to methoxypolyethylene glycol (mPEG). The strength of Loargys indicates the amount of arginase component of Pegzilarginase without considering the mPEG carrier. The strength of this medicine should not be compared with that of another pegylated or non-pegylated protein of the same therapeutic class. Loargys is used for the treatment of Arginase-1 deficiency in adults, adolescents, and children aged 2 years and older. Treatment should be initiated and monitored by a physician experienced in the treatment of inherited metabolic disorders [32-34]. Loargys is intended for the chronic treatment of patients with ARG1-D in conjunction with individualized disease management, such as protein restriction in the diet, amino acid supplements, and pharmacological treatment, including nitrogen scavengers. Loargys should be administered by intravenous infusion or subcutaneous injection, with the dose being the same. In clinical studies, treatment was initiated intravenously and then switched to subcutaneous administration (after at least 8 weeks). Each 0.4 ml vial contains 2 mg Pegzilarginase (5 mg Pegzilarginase per ml). Each 1 ml vial contains 5 mg Pegzilarginase (5 mg Pegzilarginase per ml). The recommended initial dose of Loargys is 0.1 mg/kg per week. The dose can be increased or decreased in increments of 0.05 mg/kg to achieve therapeutic goals. Doses above 0.2 mg/kg/week have not been studied in clinical trials for ARG1-D. Before starting treatment, a baseline plasma arginine concentration should be determined. After starting treatment, the weekly dose should be adjusted based on arginine concentrations prior to administration to maintain plasma arginine concentration within the normal range. To maximize time within the normal range, dose adjustments should aim to achieve a plasma arginine concentration close to the upper limit of normal before dosing. Dose adjustment should typically be based on two consecutive measurements, with such assessment being done initially after 4 weeks of use. It is recommended to monitor plasma arginine levels weekly for a period of 2 weeks after each dose adjustment to assess the effects of dose change. Once the individual dosage has been established, it is recommended to monitor plasma arginine concentration in accordance with routine clinical visits at intervals of no more than 3-6 months. For patients treated with Loargys, validated methods should be used to monitor arginine levels, as standard methods are not sufficient to control the remaining enzyme activity of Pegzilarginase after sampling, and can lead to falsely low arginine levels and incorrect dose adjustments. If a dose is missed, Loargys should be given as soon as possible. Patients should not be given 2 doses to make up for the missed dose, and there should be at least 4 days between doses. It is not expected that impaired liver function will affect the recommended dosing schedule for Loargys. The safety and efficacy of Loargys in patients with impaired renal function have not been established. There are no data available. It is not expected that impaired renal function will affect the recommended dosing schedule for Loargys. The dosage for children and adolescents aged 2 years and older is the same as for adults. The safety and efficacy of Loargys in children under 2 years of age have not been established. There are no data available. Loargys is intended for intravenous infusion or subcutaneous injection. If appropriate, after at least 8 weeks of treatment, subcutaneous administration by the patient or caregiver may be considered once a stable maintenance dose has been determined and the risk of hypersensitivity reactions is deemed low. Before self-administration, the patient or caregiver should receive appropriate training on the correct administration technique.

There is currently, as of early 2026, no approved gene therapy that permanently cures the genetic defect [35,36]. However, research is intensively focused on gene therapy approaches, while in February 2026, a new enzyme replacement therapy received FDA approval in the USA. Pegzilarginase is a recombinant enzyme administered once weekly that replaces the function of the defective enzyme to break down arginine. This new therapy option does not cross the blood brain barrier. Research on gene therapies show preclinical studies that are investigating the use of Adeno-Associated Viral Vectors (AAV) to deliver a functional ARG1 gene into liver cells [37,23]. The goal is to restore enzyme production in the body, which led to a cure in mice. In addition to traditional gene therapies, research is also being conducted on mRNA-based approaches that temporarily provide cells with the information to produce the enzyme [37,38]. Since Arginase-1 deficiency leads to neurological damage, a gene therapy that only acts in the liver may not be sufficient to reverse already existing brain damage. In summary, while the new enzyme replacement therapy Pegzilarginase (Loargys) is changing the standard of treatment in 2026, but to date, does not cross the blood brain barrier and therefore does not have influence on cognitive impairment. The actual gene therapy for curing ARG1-D remains a research goal. In cancer management, arginase inhibitors alone or with pembrolizumab were introduced [39]. Future research is focusing on next generation enzyme replacement therapy with crossing the blood brain barrier and new gene therapy options with AAV gene delivery or CRISPcas9-technology to repair the mutation in a one-time approach for the future [40-46].

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Conflict of Interest

None.

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