Accepted Manuscript online: 2025-01-07 Article published online: 2025-01-21

Intravitreal Enzyme Replacement Therapy Slows Retinopathy in Late Infantile Ceroid Lipofuscinosis Type 2

Claudia S. Priglinger[1] Carolina Courage[2] Amelie S. Lotz-Havla[3] Maximilian Gerhardt[1] Oliver Ehrt[1] Matthias Kurz[4] Harald Pudritz[5] Günther Rudolph[1] Christopher B. Jackson[6] Esther M. Maier[3,7]

[1] Department of Ophthalmology, LMU University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany
[2] Folkhälsan Research Center, Helsinki, Finland
[3] Department of Inborn Errors of Metabolism, Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University Munich, Munich, Germany
[4] Department of Anesthesiology, LMU University Hospital, Ludwig-Maximilians-University Munich, Germany
[5] Department of Pharmacy, LMU University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany

Address for correspondence Prof. Dr. med. Esther M. Maier, Department of Inborn Errors of Metabolism, Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University, Lindwurmstr. 4, 80337 Munich, Germany (e-mail: esther.maier@med.uni-muenchen.de).

[6] Department of Biochemistry and Developmental Biology, Faculty of Medicine, University of Helsinki, Helsinki, Finland
[7] Labor Becker MVZ GbR, Newborn Screening Unit, Munich, Germany

Neuropediatrics

Abstract

Ceroid lipofuscinosis type 2 (CLN2) is caused by biallelic pathogenic variants in the *TPP1* gene, encoding lysosomal tripeptidyl peptidase 1 (TPP1). The classical late-infantile phenotype has an age of onset between 2 and 4 years and is characterized by psychomotor regression, myoclonus, ataxia, blindness, and shortened life expectancy. Vision loss occurs due to retinal degeneration, usually when severe neurological symptoms are already evident.

Intracerebroventricular enzyme replacement therapy (ICV-ERT) using recombinant human TPP1 (rhTPP-1) was shown to slow the neurological decline; however, it does not prevent loss of vision. Intravitreal rhTPP-1 (IVT-ERT) was described to halt retinal degeneration in a canine CLN2 model and a compassionate-use study in humans.

We report on the clinical and ophthalmological outcome in an early-treated patient homozygous for a pathogenic variant in *TPP1* known to be associated with severe CLN2 retinopathy.

He was started on ICV-ERT at the age of 40 months and 4 weekly IVT-ERT in one eye at the age of 60 months. The other eye served as untreated control.

Baseline best corrected visual acuity (BCVA) was 0.5 with mild bull's eye maculopathy evident in both eyes. After 24 months of IVT-ERT, BCVA in the treated eye was 0.2 with bull's eye maculopathy sparing outer retinal layers, whereas the untreated eye had progressed to endstage retinopathy and BCVA <0.02. No intraocular side effects occurred.

Our results provide further evidence that IVT-ERT appears to be safe and markedly delays retinal degeneration preserving visual function and increasing the patient's quality of life, especially if started early.

Keywords
- neuronal ceroid lipofuscinosis
- ceroid lipofuscinosis type 2
- intracerebroventricular enzyme replacement therapy
- retinopathy
- intravitreal enzyme replacement therapy
- cerliponase alfa

received
October 21, 2024
accepted after revision
December 2, 2024
accepted manuscript online
January 7, 2025

DOI https://doi.org/10.1055/a-2510-5592.
ISSN 0174-304X.

Georg Thieme Verlag KG, Oswald-Hesse-Straße 50, 70469 Stuttgart, Germany

Introduction

Neuronal ceroid lipofuscinoses (CLNs) comprise a group of 13 rare, inherited lysosomal storage disorders clinically characterized by cognitive and motor regression, myoclonus, ataxia, loss of vision, and shortened life expectancy.[1,2] The age of onset is typically during childhood but varies between CLN types. Together, CLNs represent the most common pediatric neurodegenerative diseases.[1]

Neuronal ceroid lipofuscinosis type 2 (CLN2 disease; OMIM#204500) is caused by biallelic pathogenic variants in the *TPP1* gene resulting in a deficiency of the enzyme tripeptidyl peptidase (TPP1),[2] which cleaves tripeptides from the amino terminus of small polypeptides marked for degradation. Its loss of function results in an accumulation of cytotoxic lipofuscin-containing storage material in lysosomes of neuronal tissue, including retinal cells of the eye.[3]

CLN2 manifests between 2 and 4 years of age and follows a largely predictable course. Symptoms typically start with an unprovoked seizure, often preceded by a history of speech delay.[4] The initial symptoms are followed by rapid language regression, onset or worsening of ataxia, and ultimately the complete loss of independent mobility due to a complex movement disorder. Intractable epilepsy, dementia, inability to swallow, and deteriorating vision mark the progress of the disease. Death usually occurs between 8 and 12 years of age.[4,5] Historically, the average onset of obvious visual symptoms was reported at an age of 48 months when cognitive and motor decline were already advanced. Loss of visual functions then follows a tilted S-shaped decline with rapid progression into blindness within 3 years.[6,7] The retinopathy has a cone-rod phenotype and is classified using the Weill Cornell Batten scale, a scoring system based on fundus appearance and optic coherence tomography (OCT) findings. The score divides ocular findings into five severity categories ranging from a normal fundus (score 1), pigmentary changes in the parafoveal region (score 2), bull's eye maculopathy extending less than one disc parameter (score 3) and more than one disc diameter from the fovea (score 4) to diffuse widespread outer retinal atrophy (score 5).[6,7]

In 2017, cerliponase alfa (BioMarin Pharmaceutical, Novato, CA, USA), a recombinant human TPP1 (rhTPP-1) enzyme, was approved for intracerebroventricular enzyme replacement therapy (ERT). The intracerebroventricular administration of cerliponase alfa has been shown to markedly slow down cognitive decline and preserve motor and language function in CLN2 patients compared with untreated historical controls.[8,9] However, the treatment has no effect on CLN2 retinopathy, most likely because the enzyme does not cross the lamina cribrosa and blood–retinal–brain barrier. Thus, CLN2 patients treated with intracerebroventricular cerliponase alfa experience a loss of visual function similar to the natural course.[10,11] As cognitive, neurological, and language decline with ERT is markedly delayed, the unaltered rapid loss of visual functions becomes a huge burden for the patients. Intriguingly, intravitreal rhTPP-1 was shown to halt retinal degeneration in a canine model of CLN2.[12] A prospective interventional controlled open-label compassionate-use study evidenced safety of 8-weekly 0.2-mg intravitreal rhTPP-1 in severely affected CLN2 patients and its efficacy in reducing the rate of macular volume loss in patients who had not yet reached endstage degeneration before the start of treatment.[13,14]

Here, we report on the clinical and ophthalmological outcome in an early-treated patient homozygous for the pathogenic variant c.509–1G > C in *TPP1*, which is known to be associated with a severe course of CLN2 retinopathy.

Clinical Case Description

The patient was born after an uneventful pregnancy to non-consanguineous parents of Caucasian descent. His psychomotor development was normal until the age of 36 months when his first seizure occurred. Genetic testing revealed the homozygous pathogenic *TPP1* variant c.509–1G > C, which is known to be associated with severe CLN2 retinopathy.[10] Determination of TPP1 activity in leukocytes was below the limit of quantitation, confirming the diagnosis at the age of 39 months. At diagnosis, the boy was evaluated neuropsychologically, cognitively, and motorically as age-appropriate.

At the age of 40 months biweekly intracerebroventricular ERT with cerliponase alfa was started. CLN2 motor and language score at first ERT was 6.[2]

At the age of 49 months, optical coherence tomography (OCT) revealed first signs of CLN2 retinopathy corresponding to an ophthalmic severity score of 2 (data not shown).[7]

Treatment with intravitreal cerliponase alfa at a dosage of 0.2 mg in 0.05 mL balanced salt solution (BSS) was started in the right eye at an age of 60 months as an individual medical treatment and applied every 4 weeks under general anesthesia. The left eye served as untreated control. The initial dose was chosen by scaling up the 0.1 mg used in the canine model[12] and increased to 0.4 mg in 0.05 mL after 8 injections. The decision to shorten the treatment interval to 4 weeks and to increase the dose after 8 injections was based on the experience of the compassionate-use study (personal communication).[13,14] The rationale was to increase the treatment effect by providing more active enzyme and to approach the intracerebroventricular treatment interval. The preparation was made from the remains of the intracerebroventricular cerliponase alfa vial of the same patient.[12–14] After each intravitreal injection mild oculopression was performed and the eye was checked for central retinal artery perfusion. Topical dexagentamicin was prescribed for 4 days after each injection. Written informed consent on the off-label nature of the intervention was obtained from the parents.

Treatment Efficacy

Neurological Impairment and Psychomotor Development

During 44 months of intracerebral ERT combined with valproic acid, no epileptic seizures occurred. At the age of 7 years, no language decline and no ataxia were obvious, resulting in a stable CLN2 motor and language score of 6.

Recently observed neurological symptoms were intention tremor and increasing myoclonus.

Visual Impairment

At baseline (age 60 months), best corrected visual acuity (BCVA) as assessed by LEA charts was 0.5 (decimal) in both eyes (►**Fig. 1**). Dilated fundus examination revealed foveal retinal pigment epithelium condensation and perifoveal mottling. Ophthalmic severity score was 3 (►**Fig. 2A**). Until intravitreal ERT 5, loss of visual acuity and structural degeneration continued bilaterally and symmetrically (►**Fig. 1** and ►**Fig. 2A**). After intravitreal ERT 8, BCVA was 0.32 in the right and 0.2 in the left eye; thus, an inter-eye difference began to become apparent. In near-infrared reflectance images the diameter of the atrophic zone in untreated left eye was larger than in the treated right eye. Also from behavioral observations, a more accelerated disease could be suspected in the untreated eye. For example, the child expressed frustration when occluding the treated eye for BCVA testing of the untreated eye. In addition, in the untreated eye, fixation had become increasingly unstable in OCT. After 2 years of intravitreal ERT, the treated right eye was still at ophthalmic severity score 3 to 4, while the untreated left eye had progressed to 5 (►**Fig. 2**). BCVA was 0.32 in the right eye, and counting fingers in the left eye (►**Fig. 1**).

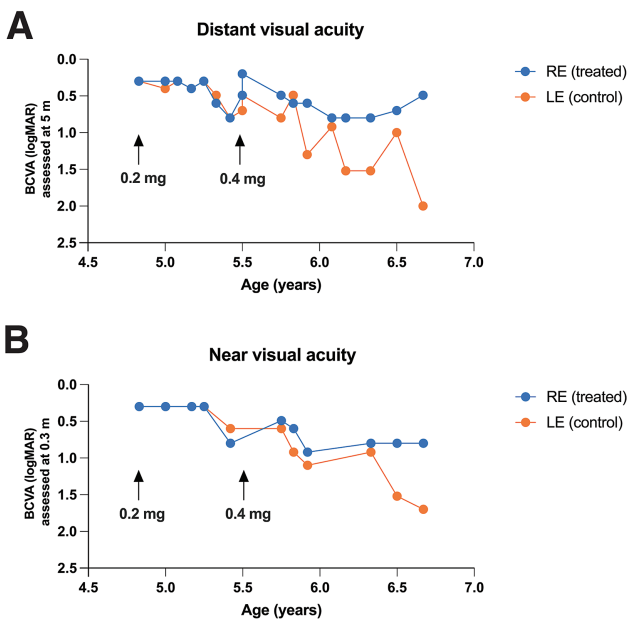

Fig. 1 Course of best corrected visual acuity (BCVA) in the treated right (RE) and untreated left (LE) eye. Intravitreal injections consisted of 0.2 mg cerliponase alfa for the first 8 injections and 0.4 mg thereafter, starting at the age of 60 months and followed up for 23 months. (**A**) Distant (5 m) and (**B**) near (30 cm) BCVA was assessed by LEA charts and converted to LogMAR. For 6 to 8 months into treatment, the BCVA followed parallel trajectories with a trend toward decline in both eyes. Thereafter, an inter-eye difference was increasingly apparent. At the end of follow-up, the treated RE reached a distant BCVA of 0.49 LogMAR (0.32 decimal) in the treated RE, whereas the untreated LE had deteriorated to 2.0 LogMAR, which is equal to counting fingers.

Treatment Safety

No relevant ocular complications occurred. In particular, no paracentesis for occlusion of the central retinal artery was required and no signs for intraocular inflammation were observed. General anesthesia was well tolerated without complications.

Discussion

This case report provides further evidence for the treatment effect of intravitreal cerliponase alfa in a child with CLN2 retinopathy. CLN2 retinopathy is a primary photoreceptor disease, where cone dysfunction is followed by combined degeneration of cones and rods. It shows an accelerated phase between 3 and 5 years of age and culminates in diffuse outer retinal atrophy leading to blindness at the age of 6 to 8 years despite intracerebroventricular ERT.[8,10,13–15] Patients homozygous for the c.509–1G > C variant have been described to experience an even more severe retinopathy.[10] Both the aggressive course of this genotype and the rapid decline during the actively degenerating phase are evident in the case presented here. Already at the age of 49 months, our patient had an ophthalmic WCBS severity score of 2. Until the start of intravitreal ERT 11 months later, retinopathy progressed to score 3 in both eyes, and the most severe score of 5 in the untreated eye 15 months later. In a patient cohort comprising other/distinct genotypes a severity score of 2 was reached at an average age of 59 months, progressing to score 3 at 69 and score 5 at 81 months.[6,7] This indicates that our patient was in the rapidly degenerating phase at the commencement of intravitreal ERT, and might explain why the therapeutic effect occurred delayed and retinopathy continued to progress quite symmetrically in both eyes for 6 to 7 months. Only thereafter, functional and structural differences between the treated eye and the untreated control eye became apparent. While the RE began to stabilize at severity score 3 to 4 and BCVA of 0.2, the untreated left eye continued to deteriorate to endstage retinopathy and BCVA of counting fingers as predicted from the natural course data.[7] An equally delayed effect of intravitreal ERT on structural retinopathy was observed in the four participants of a compassionate-use study, who were assumed to be in the actively degenerating phase at the beginning of treatment. They showed a significant inter-eye difference with slowing down of paracentral macular volume reduction in the treated eye after 6 to 8 months of continuing decline in both eyes.[13,14] The compassionate-use study, however, was performed on severely affected patients. Thus, visual acuities could not be assessed. In contrast, our patient was treated early with intracerebroventricular ERT and remarkably compliant for his age. Therefore, reliable testing of visual acuity was reproducibly possible and enabled us to describe, for the first time, the functional effects of intravitreal ERT corresponding to the structural/anatomical effects.

In conclusion, we add to the assumption that intravitreal cerliponase alfa is able to delay CLN2 retinopathy, probably most effectively if begun before first signs of photoreceptor involvement are evident.[13] Equally important, we show that intravitreal cerliponase alfa not only slows down anatomical

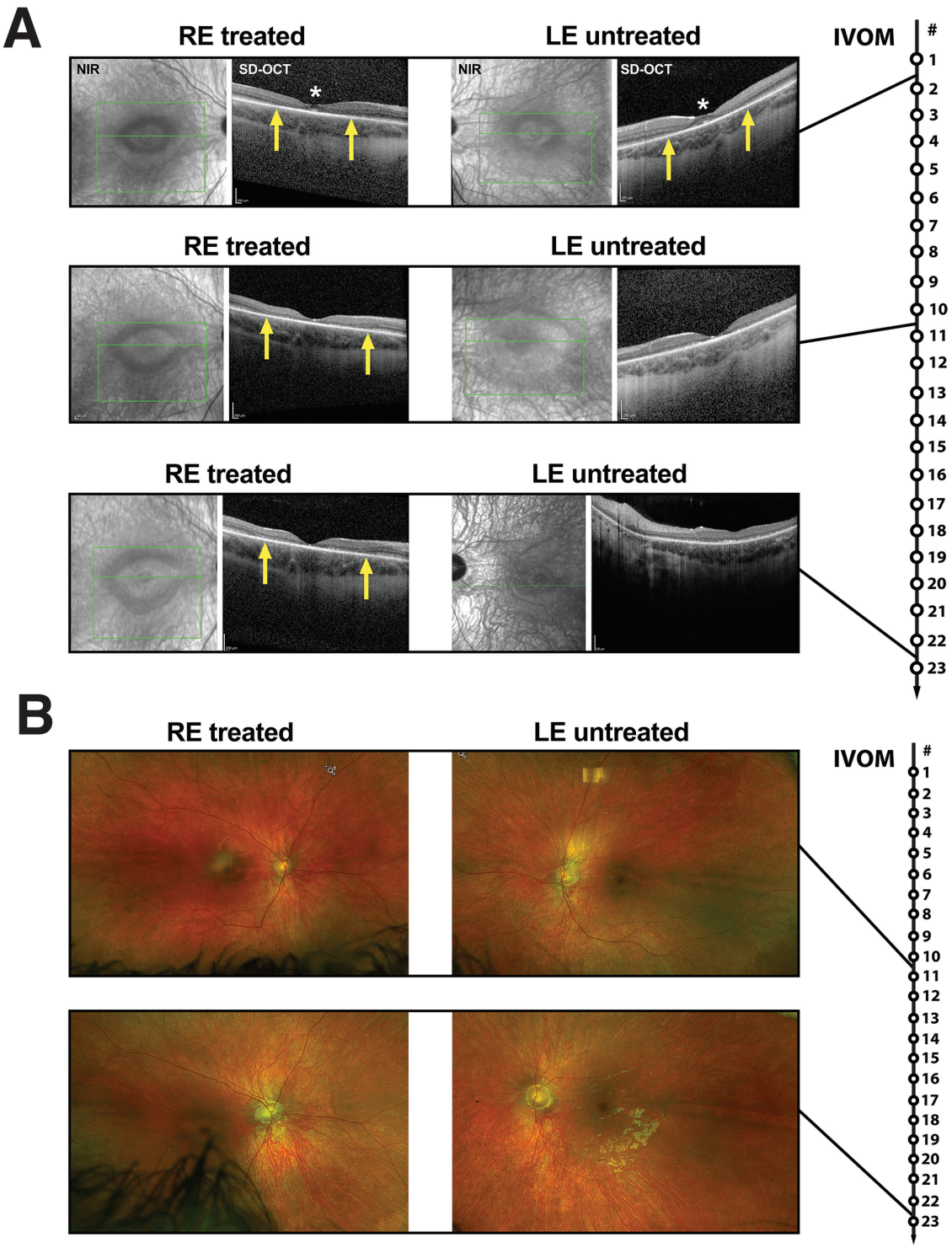

Fig. 2 Near-infrared fundus and ultra-wide field retinal imaging over the time course of intravitreal injections of cerliponase alfa into the right eye (RE). (**A**) Near-infrared (NIR) fundus images of the posterior pole obtained via confocal scanning laser ophthalmoscope and spectral domain-optical coherence tomography (SD-OCT) imaging were used to monitor intravitreal enzyme replacement therapy. At the beginning of treatment, in the NIR imaging a symmetric bull's eye maculopathy is discernible in both the treated right eye (RE) and untreated left eye (LE). SD-OCT demonstrates parafoveal outer nuclear layer thinning and disruption of the ellipsoid zone (yellow arrows) in both eyes with well-preserved subfoveal ellipsoid zone (asteriks) correlating to a severity score of 3 according to the Weill Cornell Batten Scale (WCBS). After eight intravitreal injections of cerliponase alfa, NIR images evidence a clear inter-eye difference with more extensive diameter of the bull's eye maculopathy in the untreated LE compared with baseline and the treated RE. This is also evident in the OCT scans, where a diffuse outer retinal atrophy is discernible in the NIR and the SD-OCT images of the untreated LE (WCBS severity score 5), while parafoveal ellipsoid zone as well as the external limiting membrane are still intact in the treated RE and still preserved until 23 months of follow-up. (**B**) Ultra-wide field retinal imaging 10 months after start of intravitreal therapy delineates pigmentary changes in the parafoveal region corresponding to bull's eye maculopathy in both eyes. At the end of follow-up, the bull's eye pattern is still discernible in the treated RE, but not in the untreated LE (second row).

retinal degeneration, but is also accompanied by a stabilization of visual acuity and that the child actively suffer from the loss of vision if left untreated. This is of high ethical relevance, because patients under intracerebroventricular ERT with cerliponase alfa experience a markedly slower cognitive decline. The younger they are at the initiation of treatment, the more they will inevitably have to experience a presumably treatable loss of visual functions that in the natural course occurs after severe cognitive decline.

Conflict of Interest

CSP: speaker's fee (Novartis) and fee for educational event (Chiesi); ALH: honoraria for educational event (Vitaflo), meeting and travel support (Nutricia), honoraria for advisory board (Immedica); EMM: research grant (Nutricia), meeting and travel support (Nutricia).

References

1 Schulz A, Kohlschütter A, Mink J, Simonati A, Williams R. NCL diseases—clinical perspectives. Biochim Biophys Acta 2013;1832 (11):1801–1806

2 Steinfeld R, Heim P, von Gregory H, et al. Late infantile neuronal ceroid lipofuscinosis: quantitative description of the clinical course in patients with CLN2 mutations. Am J Med Genet 2002; 112(04):347–354

3 Schaefers J, van der Giessen LJ, Klees C, et al. Presymptomatic treatment of classic late-infantile neuronal ceroid lipofuscinosis with cerliponase alfa. Orphanet J Rare Dis 2021;16(01):221

4 Nickel M, Simonati A, Jacoby D, et al. Disease characteristics and progression in patients with late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2) disease: an observational cohort study. Lancet Child Adolesc Health 2018;2(08):582–590

5 Dozières-Puyravel B, Nasser H, Elmaleh-Bergès M, et al. Paediatric-onset neuronal ceroid lipofuscinosis: first symptoms and presentation at diagnosis. Dev Med Child Neurol 2020;62(04): 528–530

6 Kovacs KD, Patel S, Orlin A, et al. Symmetric age association of retinal degeneration in patients with CLN2-associated Batten disease. Ophthalmol Retina 2020;4(07):728–736

7 Orlin A, Sondhi D, Witmer MT, et al. Spectrum of ocular manifestations in CLN2-associated batten (Jansky-Bielschowsky) disease correlate with advancing age and deteriorating neurological function. PLoS One 2013;8(08):e73128

8 Schulz A, Ajayi T, Specchio N, et al. CLN2 Study Group. Study of intraventricular cerliponase alfa for CLN2 disease. N Engl J Med 2018;378(20):1898–1907

9 Schulz A, Specchio N, de Los Reyes E, et al. Safety and efficacy of cerliponase alfa in children with neuronal ceroid lipofuscinosis type 2 (CLN2 disease): an open-label extension study. Lancet Neurol 2024;23(01):60–70

10 Thompson DA, Handley SE, Henderson RH, Marmoy OR, Gissen P. An ERG and OCT study of neuronal ceroid lipofuscinosis CLN2 Battens retinopathy. Eye (Lond) 2021;35(09):2438–2448

11 Dulz S, Schwering C, Wildner J, et al. Ongoing retinal degeneration despite intraventricular enzyme replacement therapy with cerliponase alfa in late-infantile neuronal ceroid lipofuscinosis type 2 (CLN2 disease). Br J Ophthalmol 2023;107(10):1478–1483

12 Whiting REH, Pearce JW, Vansteenkiste DP, et al. Intravitreal enzyme replacement preserves retinal structure and function in canine CLN2 neuronal ceroid lipofuscinosis. Exp Eye Res 2020; 197:108130

13 Wawrzynski J, Martinez AR, Thompson DA, et al. First in man study of intravitreal tripeptidyl peptidase 1 for CLN2 retinopathy. Eye (Lond) 2024;38(06):1176–1182

14 Rodriguez-Martinez AC, Wawrzynski J, Henderson RH. Intravitreal enzyme replacement for inherited retinal diseases. Curr Opin Ophthalmol 2024;35(03):232–237

15 Rigaudière F, Nasser H, Pichard-Oumlil S, et al. Evolution of the retinal function by flash-ERG in one child suffering from neuronal ceroid lipofuscinosis CLN2 treated with cerliponase alpha: case report. Doc Ophthalmol 2021;143(01):99–106

