A Brief Clinical Overview of Retinitis Pigmentosa

Subjects: Ophthalmology

Contributor: Kevin Yang Wu, An Qi Xu, Ananda Kalevar, Jasmeet Dhaliwal, Asif Jamal, Shrieda Jain, Simon D. Tran

Retinitis pigmentosa (RP) is a hereditary disease that causes the degeneration of photoreceptor cells in the retina, starting with the rods, leading to a gradual loss of vision over time. RP is the most common type of inherited retinal dystrophy and affects over 1.5 million people worldwide, leading to a high burden on patients and society. Common symptoms of RP include nyctalopia and gradual loss of peripheral vision, which can ultimately lead to blindness. RP is one of the primary causes of visual disability and blindness in individuals under 60 years old.

Keywords: retinitis pigmentosa ; ER stress ; retinal degeneration ; photoreceptor cell death ; therapeutictarget ; neuroprotection ; optogenetics ; gene therapy ; stem cell therapy ; preclinical studies

1. Overview of Retinitis Pigmentosa

1.1. Classification

1.1.1. Retinitis pigmentosa (RP) can be classified into two categories: syndromic and non-syndromic.

Non-syndromic retinitis pigmentosa (RP) affects only the retina, with a prevalence of 1:5000 and can be caused by sporadic mutations or genetic predisposition [1]. The mode of inheritance is classified as autosomal dominant, autosomal recessive, or X-linked [2]. Genetic testing and family history are essential tools in determining the inheritance pattern and risk for RP.

Syndromic RP refers to a group of retinitis pigmentosa conditions, including Leber Congenital Amaurosis (LCA), Usher syndrome, and Bardet-Biedl syndrome. LCA is mainly inherited in an autosomal recessive pattern and is caused by mutations in the RPE65 gene. It is characterized by early vision loss, abnormal pupillary response, and nystagmus, typically appearing in infancy. Usher syndrome is the most common syndromic form of RP, affecting about 3 in every 100,000 people. It presents with typical RP symptoms, accompanied by varying levels of hearing and vestibular dysfunction depending on the subtype [3]. Bardet-Biedl syndrome is the second most frequent syndromic form of RP, with a prevalence of 1 in every 160,000 Northern Europeans [4]. It is caused by mutations in the BBS1-BBS21 genes, with BBS1 being the most common. This autosomal recessive disease is characterized by multisystemic symptoms, including polydactyly, genital abnormality, cognitive impairment, and classic RP symptoms that usually appear in the first decade of life.

Only two types of syndromic RP have clinically significant treatments to preserve vision, despite several rare forms being present [5]. Bassen-Kornzweig syndrome is an autosomal recessive disorder characterized by retinal and neurological degeneration due to deficiencies of vitamins A and E [6]. Vitamin A (300 IU/kg/day) and vitamin E (100 IU/kg/day) supplementation has been shown to slow retinal degeneration if started early [7]. Refsum disease, on the other hand, can be managed through weight control and restriction of phytanic acid-containing foods, as the accumulation of this acid is the primary cause of retinal and neurological degeneration due to a defective enzyme [7].

1.2. Signs and symptoms

The diagnostic of Retinitis Pigmentosa (RP) is based on clinical manifestations such as nyctalopia, peripheral visual field loss, and characteristic fundus changes. The diagnosis of RP is confirmed through abnormal electroretinogram (ERG) results. The typical fundus changes in RP include bone spicules hyperpigmentation and hypopigmentation, waxy disc pallor, and arteriolar narrowing. Additionally, there are two atypical fundus phenotypes, which are retinitis punctata albescens and choroideremia [8].

1.3. Management and Prognosis

RP's prognosis is challenging to establish due to the heterogeneity of gene mutations, leading to varied disease progression. Symptoms may onset in childhood or adulthood, and visual field loss progresses annually by 4-12% [9]. Autosomal dominant RP typically results in the least severe vision loss, whereas X-linked RP has the most severe manifestations and the worst prognosis [10]. The progression of visual field loss in RP generally begins with sectorial scotoma in the mid-peripheral areas, advancing to partial ring scotoma, complete ring scotoma, and ultimately culminating in total blindness. Standard medical follow-up for RP patients includes annual ophthalmic examination, which measures visual acuity and Goldmann visual field, dilated fundoscopy, optical coherence tomography (OCT), and occasionally fluorescein angiography (FA). Although ERG's a and b wave amplitude decline is a sensitive tool for assessing RP progression, it is not always necessary for annual follow-up [8].

Most RP patients will not become completely blind, as they retain some macular function even in their fourth decade of life [8]. In the panretinal dystrophy stage, RP patients commonly exhibit optic nerve head drusen, cystoid macular edema, vitreous cells, epiretinal membranes, and posterior subcapsular cataracts. Diminished visual acuity is often caused by the complications of cystoid macular edema and posterior capsular opacification.

Most patients with RP have no curative treatment available. Only patients with RPE65 gene mutation are eligible to receive target gene therapy. Conventional treatment options, such as vitamin A supplements, protection from sunlight, visual aids, and medical and surgical interventions, aim to manage symptoms, prevent ophthalmic complications, and slow the progression of the disease. However, these interventions do not provide a cure for the disease.

2. Conventional Treatments and Limitations

2.1. Dietary Supplements (Vitamin A, DHA, Lutein)

Vitamin A is a fat-soluble vitamin that plays an important role in visual cycle, retinal pigment epithelium cell metabolism, and phototransduction [11]. Multiple randomized clinical trials on RP patients investigated the efficacy of vitamin A, DHA, and lutein as treatments. Vitamin A alone may slow the decline of ERG amplitude but did not significantly improve visual field area or visual acuity [12]. DHA did not show significant benefits when combined with vitamin A, but a subgroup analysis showed a slower visual field decline [13]. Lutein combined with vitamin A only resulted in a slower rate of decline in the total point score for the HFA 60-4 program [14]. Despite mixed results, the combination of vitamin A, lutein, and fish oil containing DHA is still recommended as therapy for RP patients. However, a systematic research concluded that there is no significant evidence to support the use of vitamin A, DHA, or a combination thereof for RP patients [11]. Regular use of high doses of Vitamin A can cause various side effects and complications [15]. Vitamin A treatment remains controversial due to its potential risks, but there is evidence supporting its effectiveness for a small, genetically distinct subgroup of RP patients with PRPH2-associated retinitis pigmentosa [16].

2.2. Cystoid Macular Edema (CME) Treatment

Cystoid macular edema (CME) is a common complication in RP cases, affecting up to 38% of patients and causing decreased visual acuity [17][18]. First-line treatments for CME include oral and topical carbonic anhydrase inhibitors, such as acetazolamide, methazolamide, dorzolamide, and brinzolamide, which have demonstrated significant benefits in multiple studies. Second-line treatments, such as intravitreal steroids injection, oral corticosteroids, anti-VEGF injection, and topical or local non-steroidal anti-inflammatory drugs (NSAIDs), have also proven to be effective pharmaceutical therapies for patients who do not respond to carbonic anhydrase inhibitors [19].

2.3. Protection from Sunlight

Due to its high metabolic rate and oxygen consumption, as well as the presence of photosensitizer molecules in the photoreceptors that are constantly exposed to light and oxidative stress, the retina is vulnerable to oxidative stress, leading to the accumulation of reactive oxygen species (ROS) in the retinal pigment epithelium (RPE). This can perpetuate a cycle of neuroinflammation and degeneration in RP, as demonstrated by multiple pathways [20]. Animal models of RP have shown that absence of light exposure was associated with a reduction in the rate of photoreceptor degeneration, while increased housing light intensity for rd10 mice accelerated retinal degeneration by activating cell death, oxidative stress pathways, and inflammatory cells [21]. Therefore, light protection may be a potential intervention to slow down the progression of the disease in some cases of RP [22]. However, there is a lack of convincing studies to confirm the hypothesis on whether sunlight deprivation slows down retinal degeneration in RP, as demonstrated by one case report of an RP patient with mono-ocular occlusion for over 40 years who had an equivalent fundus in both eyes.

2.4. Auxiliary Support

2.4.1. External Device

Visual aids can improve the quality of life of RP patients, such as night vision pocketscopes, goggles, or light-amplifying devices that can alleviate night blindness [23][24][25]. In a study by Ikeda et al. (2015), a research device designed to assist patients with RP-induced night blindness was found to be effective. The device was equipped with a camera that provided a minimum illuminance of 0.08 lux, and the subjects using the device achieved significantly higher success rates in completing a walking task in dimly lit rooms [26].

2.5. Surgicaly Implanted Device

ARGUS II prosthesis is an option for end-stage RP patients with bare light perception, but implantation of an epiretinal device is an invasive surgery, and only limited RP patients are candidates [27]. While participants in a phase II clinical trial of the ARGUS II had significantly better scores in all visual function tests, more than one-third of them experienced serious adverse events related to the device or surgery. Furthermore, the device is only beneficial for end-stage RP patients in allowing them to restore minimal vision, and RP patients with mild visual impairment would not benefit from it to restore normal vision [28]. Nonetheless, a recent study found that the safety profile of the Argus II has significantly improved compared to the pre-approval phase, with no significant issues reported up to four years post-implantation [29].

Overall, the conventional treatments listed above have limitations, and most of them do not target the underlying pathogenesis of RP.

3. Recent Therapeutic Advances

Gene therapy is a promising approach for treating RP, targeting the genetic causes of the condition.

Currently, Luxturna is the only approved gene therapy for RP, authorized only for a small sub-population of RP patients with the RPE65 gene mutation. This mutation is responsible for vitamin A metabolism and Leber congenital amaurosis (LCA). A phase III clinical trial demonstrated significant visual function improvement and no serious adverse events after one year with voretigene neparvovec, an adeno-associated virus (AAV2) vector containing modified human RPE65, and durability of improvement after three to four years of follow-up [30][31][32]. This success has led to ongoing clinical trials targeting other gene mutations associated with RP.

References

1. O’Neal, T.B.; Luther, E.E. Retinitis Pigmentosa. In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2022.
2. Hartong, D.T.; Berson, E.L.; Dryja, T.P. Retinitis Pigmentosa. Lancet 2006, 368, 1795–1809.
3. Kimberling, W.J.; Hildebrand, M.S.; Shearer, A.E.; Jensen, M.L.; Halder, J.A.; Trzupek, K.; Cohn, E.S.; Weleber, R.G.; Stone, E.M.; Smith, R.J.H. Frequency of Usher Syndrome in Two Pediatric Populations: Implications for Genetic Screening of Deaf and Hard of Hearing Children. Genet. Med. Off. J. Am. Coll. Med. Genet. 2010, 12, 512–516.
4. Weihbrecht, K. Bardet-Biedl Syndrome. In Genetics and Genomics of Eye Disease; Elsevier: Amsterdam, The Netherlands, 2020; pp. 117–136. ISBN 978-0-12-816222-4.
5. Von Sallmann, L.; Gelderman, A.H.; Laster, L. Ocular Histopathologic Changes in a Case of A-Beta-Lipoproteinemia (Bassen-Kornzweig Syndrome). Doc. Ophthalmol. Adv. Ophthalmol. 1969, 26, 451–460.
6. Grant, C.A.; Berson, E.L. Treatable Forms of Retinitis Pigmentosa Associated with Systemic Neurological Disorders. Int. Ophthalmol. Clin. 2001, 41, 103–110.
7. Gibberd, F.B.; Billimoria, J.D.; Goldman, J.M.; Clemens, M.E.; Evans, R.; Whitelaw, M.N.; Retsas, S.; Sherratt, R.M. Heredopathia Atactica Polyneuritiformis: Refsum’s Disease. Acta Neurol. Scand. 1985, 72, 1–17.
8. Retinitis Pigmentosa: Study Guide. Available online: https://www.aao.org/Assets/bcc226cb-7ac7-443c-897e-9b20afdfacfb/637153836910470000/r38u-pdf?inline=1&fbclid=IwAR2oP_lD1pWSAROpIfa9poqhZzeSf29_PvZztBZMSQfWKNqTbv1b6t0BXJU (accessed on 15 December 2022).
9. Berson, E.L.; Sandberg, M.A.; Rosner, B.; Birch, D.G.; Hanson, A.H. Natural Course of Retinitis Pigmentosa over a Three-Year Interval. Am. J. Ophthalmol. 1985, 99, 240–251.

10. Cross, N.; van Steen, C.; Zegaoui, Y.; Satherley, A.; Angelillo, L. Retinitis Pigmentosa: Burden of Disease and Current Unmet Needs. Clin. Ophthalmol. 2022, 16, 1993–2010.
11. Rayapudi, S.; Schwartz, S.G.; Wang, X.; Chavis, P. Vitamin A and Fish Oils for Retinitis Pigmentosa. Cochrane Libr. Cochrane Rev. 2013, 2013, CD008428.
12. Berson, E.L. Retinitis Pigmentosa. The Friedenwald Lecture. Investig. Ophthalmol. Vis. Sci. 1993, 34, 1659–1676.
13. Berson, E.L.; Rosner, B.; Sandberg, M.A.; Weigel-DiFranco, C.; Moser, A.; Brockhurst, R.J.; Hayes, K.C.; Johnson, C.A.; Anderson, E.J.; Gaudio, A.R.; et al. Further Evaluation of Docosahexaenoic Acid in Patients with Retinitis Pigmentosa Receiving Vitamin A Treatment: Subgroup Analyses. Arch. Ophthalmol. 2004, 122, 1306–1314.
14. Berson, E.L.; Rosner, B.; Sandberg, M.A.; Weigel-DiFranco, C.; Brockhurst, R.J.; Hayes, K.C.; Johnson, E.J.; Anderson, E.J.; Johnson, C.A.; Gaudio, A.R.; et al. Clinical Trial of Lutein in Patients with Retinitis Pigmentosa Receiving Vitamin A. Arch. Ophthalmol. 2010, 128, 403–411.
15. Russell, R.M. The Vitamin A Spectrum: From Deficiency to Toxicity. Am. J. Clin. Nutr. 2000, 71, 878–884.
16. Pierce, E.A.; Bujakowska, K.M.; Place, E.; Navarro-Gomez, D.; Maher, M.; Weigel-DFranco, C.; Comander, J. The Effect Of Vitamin A On Progression Of Retinitis Pigmentosa Is Not Determined By The Underlying Genetic Cause Of Disease. Investig. Ophthalmol. Vis. Sci. 2017, 58, 2011.
17. Hajali, M.; Fishman, G.A.; Anderson, R.J. The Prevalence of Cystoid Macular Oedema in Retinitis Pigmentosa Patients Determined by Optical Coherence Tomography. Br. J. Ophthalmol. 2008, 92, 1065–1068.
18. Ozdemir, H.; Karacorlu, M.; Karacorlu, S. Intravitreal Triamcinolone Acetonide for Treatment of Cystoid Macular Oedema in Patients with Retinitis Pigmentosa. Acta Ophthalmol. Scand. 2005, 83, 248–251.
19. Bakthavatchalam, M.; Lai, F.H.P.; Rong, S.S.; Ng, D.S.; Brelen, M.E. Treatment of Cystoid Macular Edema Secondary to Retinitis Pigmentosa: A Systematic Review. Surv. Ophthalmol. 2018, 63, 329–339.
20. Gallenga, C.E.; Lonardi, M.; Pacetti, S.; Violanti, S.S.; Tassinari, P.; Di Virgilio, F.; Tognon, M.; Perri, P. Molecular Mechanisms Related to Oxidative Stress in Retinitis Pigmentosa. Antioxidants 2021, 10, 848.
21. Naash, M.L.; Peachey, N.S.; Li, Z.Y.; Gryczan, C.C.; Goto, Y.; Blanks, J.; Milam, A.H.; Ripps, H. Light-Induced Acceleration of Photoreceptor Degeneration in Transgenic Mice Expressing Mutant Rhodopsin. Investig. Ophthalmol. Vis. Sci. 1996, 37, 775–782.
22. Kutsyr, O.; Sánchez-Sáez, X.; Martínez-Gil, N.; de Juan, E.; Lax, P.; Maneu, V.; Cuenca, N. Gradual Increase in Environmental Light Intensity Induces Oxidative Stress and Inflammation and Accelerates Retinal Neurodegeneration. Investig. Ophthalmol. Vis. Sci. 2020, 61, 1.
23. Berson, E.L.; Rabin, A.R.; Mehaffey, L. Advances in Night Vision Technology. A Pocketscope for Patients with Retinitis Pigmentosa. Arch. Ophthalmol. 1973, 90, 427–431.
24. Hartong, D.T.; Jorritsma, F.F.; Neve, J.J.; Melis-Dankers, B.J.M.; Kooijman, A.C. Improved Mobility and Independence of Night-Blind People Using Night-Vision Goggles. Investig. Ophthalmol. Vis. Sci. 2004, 45, 1725–1731.
25. Mancil, R.M.; Mancil, G.L.; King, E.; Legault, C.; Munday, J.; Alfieri, S.; Nowakowski, R.; Blasch, B.B. Improving Nighttime Mobility in Persons with Night Blindness Caused by Retinitis Pigmentosa: A Comparison of Two Low-Vision Mobility Devices. J. Rehabil. Res. Dev. 2005, 42, 471–486.
26. Ikeda, Y.; Suzuki, E.; Kuramata, T.; Kozaki, T.; Koyama, T.; Kato, Y.; Murakami, Y.; Enaida, H.; Ishibashi, T. Development and Evaluation of a Visual Aid Using See-through Display for Patients with Retinitis Pigmentosa. Jpn. J. Ophthalmol. 2015, 59, 43–47.
27. Humayun, M.S.; Dorn, J.D.; da Cruz, L.; Dagnelie, G.; Sahel, J.-A.; Stanga, P.E.; Cideciyan, A.V.; Duncan, J.L.; Eliott, D.; Filley, E.; et al. Interim Results from the International Trial of Second Sight's Visual Prosthesis. Ophthalmology 2012, 119, 779–788.
28. da Cruz, L.; Dorn, J.D.; Humayun, M.S.; Dagnelie, G.; Handa, J.; Barale, P.-O.; Sahel, J.-A.; Stanga, P.E.; Hafezi, F.; Safran, A.B.; et al. Five-Year Safety and Performance Results from the Argus II Retinal Prosthesis System Clinical Trial. Ophthalmology 2016, 123, 2248–2254.
29. Arevalo, J.F.; Al Rashaed, S.; Alhamad, T.A.; Al Kahtani, E.; Al-Dhibi, H.A.; for the KKESH Collaborative Retina Study Group; Mura, M.; Al Kahtani, E.; Nowilaty, S.; Al Rashaed, S.; et al. Argus II Retinal Prosthesis for Retinitis Pigmentosa in the Middle East: The 2015 Pan-American Association of Ophthalmology Gradle Lecture. Int. J. Retin. Vitr. 2021, 7, 65.
30. Russell, S.; Bennett, J.; Wellman, J.A.; Chung, D.C.; Yu, Z.-F.; Tillman, A.; Wittes, J.; Pappas, J.; Elci, O.; McCague, S.; et al. Efficacy and Safety of Voretigene Neparvovec (AAV2-HRPE65v2) in Patients with RPE65-Mediated Inherited Retinal Dystrophy: A Randomised, Controlled, Open-Label, Phase 3 Trial. Lancet 2017, 390, 849–860.

31. Maguire, A.M.; Russell, S.; Wellman, J.A.; Chung, D.C.; Yu, Z.-F.; Tillman, A.; Wittes, J.; Pappas, J.; Elci, O.; Marshall, K.A.; et al. Efficacy, Safety, and Durability of Voretigene Neparvovec-Rzyl in RPE65 Mutation-Associated Inherited Retinal Dystrophy: Results of Phase 1 and 3 Trials. Ophthalmology 2019, 126, 1273–1285.
32. Maguire, A.M.; Russell, S.; Chung, D.C.; Yu, Z.-F.; Tillman, A.; Drack, A.V.; Simonelli, F.; Leroy, B.P.; Reape, K.Z.; High, K.A.; et al. Durability of Voretigene Neparvovec for Biallelic RPE65-Mediated Inherited Retinal Disease: Phase 3 Results at 3 and 4 Years. Ophthalmology 2021, 128, 1460–1468.

Retrieved from https://encyclopedia.pub/entry/history/show/99879