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REVIEW ARTICLE

RECENT THERAPEUTIC ADVANCES & PRECLINICAL PHASES OF RETINITIS PIGMENTOSA

Dr. Jitendra Kumar[1], Dr. Amit Rao[2] and Dr. Shikha Tolia[2]

1. Professor & Head, Dept. of Ophthalmology, MLB Medical College, Jhansi, Uttar Pradesh - 284001, India.
2. Junior Resident, Dept. of Ophthalmology, MLB Medical College, Jhansi, Uttar Pradesh - 284001, India.

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Abstract

Retinitis pigmentosa (RP) is a group of hereditary illnesses characterized by a slow loss of retinal photoreceptors, which impairs a long-term vision. It is among the most prevalent forms of hereditary retinal dystrophy and has a sizable cost impact on both the individuals affected and the community as a whole. The typical symptoms of this disorder include nyctalopia, loss of the concentric visual field, and finally loss of the bilateral central vision.The primary effect is a progressive loss of vision. One of the main causes of vision loss and blindness in persons under 60, it affects roughly 1.5 million people globally. There is presently no known cure for RP, and the only approved gene therapy, voretigeneneparvovec, is only given to a tiny subset of patients with known RPE65 mutations. Retinoids, vitamin A supplements, sun protection, visual aids, and medical and surgical treatments to treat ocular comorbidities are now the only available therapies, however these merely serve to halt the disease's progression. Given the limited therapeutic landscape, it is vital to develop fresh, personalized therapy modalities that focus on degeneration of the retina. Although the variety of the gene mutations involved makes it difficult to identify a target treatment for RP, new fundamental research indicates an improvement towards comprehending the causes of retinal degeneration. Discovering novel molecular treatments that can specifically target specific receptors or signaling pathways lays the foundation for more effective medication development. The most recent advancements in potential RP treatments are highlighted in this article, with an emphasis on preclinical stage foundational research on molecular targets, which will form the basis for subsequent drug development. We will discuss the alterations that take place to the molecular pathways connected to the growth of RP, with a focus on the ER stress and apoptotic pathways, redox balance maintenance, and genomic stability. Subsequently proceed over the treatment modalities being looked at, like gene and cell therapy, as well as the most recent studies that are discovering new potential drug targets for RP.

Corresponding Author:- Dr. Jitendra Kumar
Address:- Professor & Head, Dept. of Ophthalmology, MLB Medical College, Jhansi, Uttar Pradesh - 284001, India.

Introduction:-

Retinitis pigmentosa (RP) is a variety of genetic disorders that cause the photoreceptor cells in the retina to progressively deteriorate, commencing with the rods. As a consequence, vision gradually deteriorates over time. It is the most common instance of hereditary retinal dystrophy and places a heavy cost on individuals as well as the general public. Over 1.5 million people are affected globally, making it one of the main causes of vision impairment and blindness in persons under 60 [1]. Nyctalopia and a progressive loss of peripheral vision that eventually results in blindness are common symptoms of RP, despite various phenotypes of the diseases.

A brief description of retinitis pigmentosa

Clinical Signs and Symptoms

A comprehensive diagnosis is the first step in Retinitis Pigmentosa (RP) management that is effective. The diagnosis of RP is made on the basis of clinical signs such nyctalopia, peripheral visual field loss, and distinctive retinal abnormalities, and is supported by abnormal ERG findings. Bone spicule hyper- and hypopigmentation, waxy disc pallor, and arteriolar constriction are examples of typical fundus alterations. The atypical fundus phenotypes retinitis punctataalbescens and choroideremia are other two that are widely known [2].

Classification

Syndromic and non-syndromic RP fall into these two groups. A prevalence of 1:5000 has been reported for non-syndromic RP, which solely affects retinal dystrophy and does not impact any other organs [3]. Sporadic mutations, the most common etiology of Retinitis Pigmentosa (RP), can cause the condition, but genetic predisposition remains the main risk factor. The manner of inheritance can be categorized as X-linked (occurring in 5-15% of cases), autosomal dominant (30–40% of cases), or autosomal recessive (50–60% of cases) [4]. For researchers to understand the pattern of inheritance and determine the risk for RP, family history and genetic testing are crucial tools. Leber Congenital Amaurosis (LCA), Usher syndrome, and Bardet-Biedl syndrome are examples of syndromic RP. The primary symptoms of LCA, which is primarily an inherited hereditary disorder caused by the RPE65 mutation, are early vision loss (from 20/200 to no light perception), congenital abnormal pupillary response, and nystagmus observed during infants. Usher syndrome is the most common syndromic form of RP (prevalence of 3:100,000), and depending on the subtype, it presents clinically with the characteristic symptoms of RP and varies in the severity of auditory and vestibular impairment [5]. With an incidence of 1:160,000 in Northern Europeans, Bardet-Biedl syndrome is the second most common syndromic variant of RP [6] (pp. 117–136). The BBS1-BBS21 gene mutations (predominantly BBS1) are the source of this autosomal recessive genetic disease, which presents as a multisystemic disorder with polydactyly, genital abnormalities, cognitive impairment, and characteristic RP symptoms within the first 10 years of life.There are several unique variants of syndromic RP, however just a few of them are clinically significant since there are several medicines that can prevent vision loss. Vitamin A and E deficiency are hallmarks of the autosomal recessive condition known as Bassen-Kornzweig syndrome, which causes retinal and neurological deterioration [7]. Regular vitamin A and vitamin E supplementation has been shown to be useful in reducing the progression of retinal degeneration [8]. Retinal and neurological degeneration in Resume disease is mostly caused by accumulation of this acid due to a faulty enzyme, which can be prevented by controlling weight and avoiding meals containing phytanic acid [9].

Management and Prognosis

Due to a variety of gene mutations, the prognosis for RP is challenging to determine. Various gene mutations and additional variables can affect how the disease develops. Despite a typical yearly increase in 4-12% visual field loss, some investigations indicated that symptoms could appear in either childhood or maturity [10]. Generally speaking, autosomal dominant RP has the least severe visual loss, whereas X-linked RP has the worst prognosis and more serious symptoms [1]. Sectorial scotoma in the mid-peripheral zones is frequently the first sign of visual field loss in RP that advances to partial ring scotoma, entire ring scotoma, or even total blindness. Yearly ocular examinations, which include measuring visual acuity and the Goldmann visual field, dilated fundoscopy, optical coherence tomography (OCT), and sporadically fluorescein angiography (FA) are all part of the standard medical follow-up for people with RP. Electroretinogram (ERG) and b wave amplitude drop are sensitive tools to monitor the development of RP, but annual follow-up may not be necessary [2].

Despite the fact that the majority of RP patients will suffer from a legal blindness in their fourth decades of life, they will still have some macular function, thus they will not become totally blind [2]. At the panretinal dystrophy stage, optic nerve head drusen, cystoid macular edema, vitreous cells, epiretinal membranes, and posterior sub capsular cataracts are typical symptoms seen. Reduced visual acuity is a common symptom of RP and is often brought on by

the side effects of posterior capsular pacification and cystoid macular edema. The majority of RP sufferers are at present not curable. The RPE65 gene mutation makes a limited subset of RP patients eligible for target gene therapy. Most RP patients use standard therapies, such as vitamin A supplements, sun protection, visual aids, and medical and surgical procedures. These therapies do not treat the underlying condition; rather, they control signs and symptoms, avoid ocular complications, and retard disease development [11].

Conventional Treatments and Limitations

Dietary Supplements (Vitamin A, DHA, Lutein)

Retinyl the ester, a type of vitamin A that is fat-soluble, is primarily deposited in the liver. It is generally recognized that various forms of vitamin A (all-trans-retinol) are essential for photo transduction, the visual cycle, and the metabolism of retinal pigment epithelium cells [12]. The usefulness of vitamin A, DHA, and lutein as therapies was investigated by Berson in numerous randomized clinical trials on RP patients. Despite not showing a significant change in visual field size or visual acuity, the data indicated that vitamin A alone may reduce the reduction of ERG amplitude [13]. When combined with vitamin A, DHA did not differ significantly from vitamin A single. A subgroup analysis of DHA, however, exhibited an accelerated loss of visual perception [14]. As a result, lupeol combined with vitamin A only resulted in a slower rate of decline in the HFA 60-4 program's overall point score [15]. Humans with RP continue to be encouraged to take vitamin A, lutein, and fish oil containing DHA despite conflicting results. However, Rayapudi et al. (2013) concluded that there was no proof that vitamin A, DHA, or a combination of the two could significantly improve RP patients after a thorough analysis of three clinical trials (Berson 1993, Berson 2004, and Hoffman 2004). Further, implementing excessive amounts of vitamin A over an extended period of time may have a number of negative effects. In addition to short-term adverse effects like nausea, loss of appetite, headaches, dizziness, exhaustion, and dry and itchy skin, these could also include long-term issues such liver toxicity, an increased risk of osteoporosis, and hip fractures [16]. The risk of teratogenicity associated with vitamin A supplementation is especially concerning for the typical RP population, where many patients are in the early stages of pregnancy. For all of the aforementioned reasons, the use of vitamin A in treatment is still contested. However, the current study suggests that a small, genetically separate subgroup of RP patients with PRPH2-associated retinitis pigmentosa may benefit from treatment [17].

Cystoid Macular Edema (CME) Treatment

In up to 38% of RP cases, cystoid macular edema (CME) can develop as an outcome, which may affect vision [18, 19]. This has been demonstrated by numerous studies to show the benefits of topical carbonic anhydrase inhibitors (dorzolamide and brinzolamide) and oral carbonic anhydrase inhibitors (acetazolamide and methazolamide) as first-line therapy. This is in accordance with Bakthavatchalam 2017's systematic review. Injections of intravitreal steroids, oral corticosteroids, and injections of an anti-VEGF, topical or local non-steroidal anti-inflammatory drugs (NSAID), and other therapies are second-line options for individuals who do not respond to carbonic anhydrase inhibitors [20]. These forms of therapy have also been shown to be successful drugs therapies.

Protection from Sunlight

Due to a rapid metabolic rate, high oxygen consumption, and the presence of chemicals that photosensitize photoreceptors to light and oxidative stress, the retina is susceptible to these conditions. The retinal pigment epithelium (RPE) begins to accumulate reactive oxygen species (ROS) as a result. There are numerous routes that have demonstrated how neuroinflammation and degeneration may cycle in RP as a result of oxidative microglial activation [21]. According to a study on RP animal models, reduced photoreceptor degradation was linked to reduced exposure to light [22]. It has been demonstrated that rd10 mice's retinal degeneration is sped up by increased housing light intensity by inducing inflammatory cells, cell death, and oxidative stress pathways. Thus, for specific RP instances, sun shielding may be a possible strategy to reduce the disease's progression [23]. An RP patient who had mono-ocular occlusion for more than 40 years, however, had a comparable retinal in both eyes, according to a case study. Therefore, there aren't enough strong research to back out the claim that RP patients' lack of sunlight accelerates retinal degeneration.

Visual Aids

The quality of life for patients may be enhanced by some visual assistance. Night blindness may be reduced, for instance, with the use of night vision goggles, pocketscopes, or other equipment that could magnify light [24–26]. The success of a research tool created especially to help people with RP-induced night blindness was established by a study by Ikeda et al. (2015). The device had a camera that produced a minimum illumination of 0.08 lux, and people who used it were much more successful at completing an outdoor task in poorly light spaces [27].

Surgical Intervention

ARGUS II prothesis is a possibility for patients with end-stage RP who have bare light perception. The epiretinal electrode chip used in the implant sends electrical impulses to the retina. On the glasses is a video recorder that records footage, converts it to electrical impulses, and sends the electrical impulses to the implant. Patients with severe vision loss can use this gadget to perceive the edges and lines of nearby objects [28]. Few RP patients are qualified for the invasive procedure needed to implant an epiretinal device. Despite having significantly better results on all visual function tests when the device was being used, more than one-third of participants in a phase II clinical trial of the ARGUS II experienced serious adverse events connected to the tool or the procedure, including conjunctival erosion, conjunctival dehiscence, hypotony, and endophthalmitis. ARGUS II prothesis, as it is, only helps patients with end-stage RP by giving them a small amount of vision back. This technology would not be useful for restoring normal vision in RP patients with modest visual impairment [29]. But according to a recent study, the Argus II's safety profile has greatly improved since the preapproval stage, and no serious problems have been observed for a maximum of four years after implantation [30]. In conclusion, each of the standard therapies mentioned above has drawbacks. Additionally, the majority of them do not focus on the pathophysiology of RP from the ground up.

Potential Therapeutic Approaches

One of the potential approaches for treating RP is gene therapy because it focuses on the underlying genetic origins of the disease. Only a small subset of patients who have the RPE65 gene mutation, resulting in up between 0.3% and 1% of all cases of RP, are permitted for treatment with Luxturna (voretigeneneparvovec), the only gene therapy for RP that has received approval to date. A mutation in the RPE65 gene, which controls the visual cycle's metabolism of vitamin A, results in the Leber congenital amaurosis (LCA) syndrome. 31 patients with verified biallelic RPE65 mutations participated in the phase III clinical trial and received voretigeneneparvovec, an adeno-associated virus (AAV2) vector containing enhanced human RPE65.During having this drug, visual function significantly improved, there were no substantial adverse events after one year, and the improvement was still there after three to four years of follow-up [31–33]. The efficacy of this gene therapy has inspired more studies into additional gene variations associated with RP. Researchers have access to a large number of active clinical trials for potential retinitis pigmentosa gene treatments on clinicaltrials.gov.

New therapeutic targets that are in the preclinical stage will be the subject of the following sections. We will discuss the molecular mechanisms underlying retinitis pigmentosa (RP) development as well as the numerous preclinical therapeutic approaches currently under investigation, such as gene therapy, cell therapy, optogenetics, neuroprotective agents, and novel treatment targets recently reported in scientific journals (Figure 1).

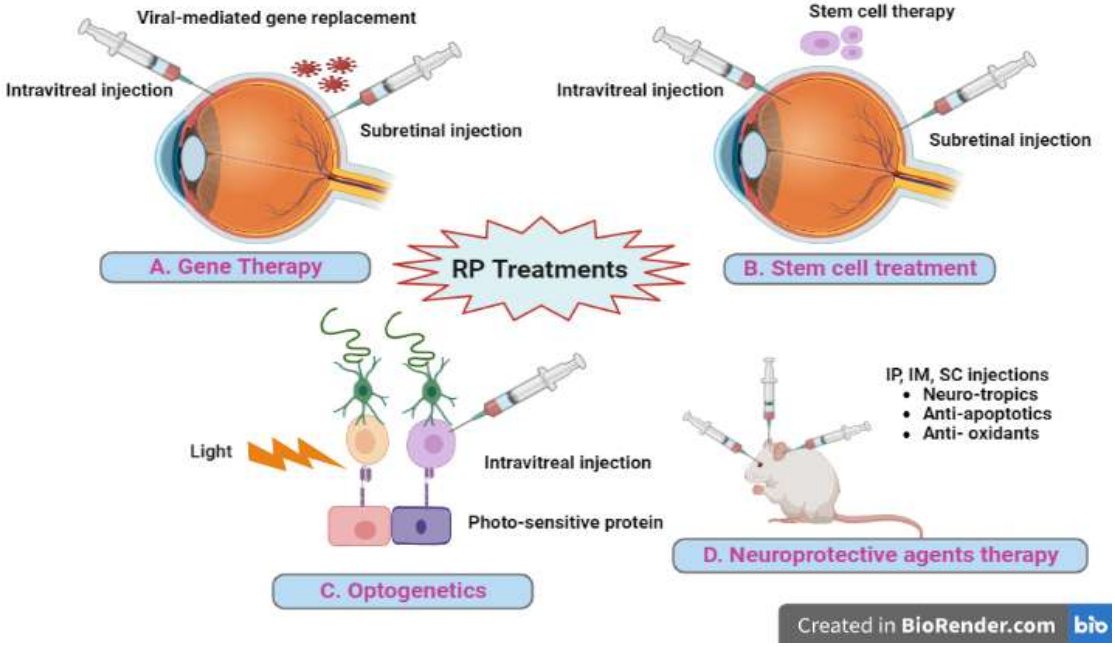

Figure 1:- Potential therapeutic modalities for retinitis pigmentosa. (**a**) Gene therapy (**b**) Stem Cell therapy (**c**) Optogenetics and (**d**) Neuroprotective agents.

Gene Therapy

Overview of Gene Therapy Methods

Gene therapy has achieved significant advances recently, especially when used to treat inherited retinal abnormalities [34]. There are essentially two gene therapy approaches that can be employed for RP, depending on the disease's pattern of inheritance. In hereditary RP, that demonstrates a loss of function of the target protein, the aim is to adopt a gene complementation technique. Gene suppression with or without gene complementation is one of the gene therapy approaches for dominant RP. To achieve the therapeutic objective of RP treatment, a number of gene therapy approaches have been developed using viral or non-viral vectors. In this section, we'll go through the many gene therapy methods that are presently being researched for developing of management strategies for RP.Targeting Retinitis Pigmentosa Pathogenesis are.

1. Autosomal Dominant-Linked Mutations
2. Autosomal Recessive-Linked Mutations
3. Identification of Gene Targets Involved in Retinitis Pigmentosa for Novel GeneTherapy Treatments

Stem Cell Therapy

Cell therapy is one of the additional methods of vision restoration. Two types of cell-based therapy are effective:
(1) To change out cells that are unhealthy for healthy stem cells.
(2) To release trophic factors in order to restore damaged cells. For cells transplanted to work, the host must long-term integrate them while developing new synaptic connections [35].

Novel Therapeutic Targets in Preclinical Phase: Optogenetics

Despite the fact that retinal gene therapies have had a lot of success over the years, there are some situations when they are unable to restore a patient's function. Patients without genetic diagnoses and those with severe disorders and no functioning photoreceptors are two examples of the limitations of gene therapy [36]. Optogenetics, on the other hand, is a generalized therapy that may be applied in situations where degradation has taken place, regardless of the precise mutation present. Optogenetics in RP is basically the process of creating artificial photoreceptors from non-photosensitive retinal cells, usually bipolar or retinal ganglion cells (RGCs). A protein that is sensitive to light, called opsin, is introduced into the cells to do this. Optogenetic methods to make cells light-sensitive have been investigated since the discovery of channelrhodopsin-2 (ChR2) [37]. Depolarized or hyperpolarized opsins can be utilised, depending on the procedures and the target cell. Depolarized opsins, on the other hand, are used on inactive cells and are used to imitate a "on" response [38]. The opsin genes used in optogenetic vision restoration are separated into two superfamilies: microbial opsins (Type 1) and animal opsins (Type 2). While both opsin families contain photoactive proteins with seven trans membranehelical domains, their light sensitivity, function, and utility for vision restoration vary [39]. Type 1 opsinsutilize the all-trans-retinal chromophore and isomerize upon light absorption to trigger a conformational alteration and directly impact ion channels or pumps [40]. Type 2 opsins frequently form a covalent bond with 11-cis-retinal, and light absorption triggers intracellular G-protein-coupled receptor (GPCR) signaling cascades that, in turn, indirectly alter ion channels [41].

Novel Therapeutic Targets in Preclinical Phase: Neuroprotective Agents

A number of therapies, particularly neuroprotective agent therapy, can halt the development of Retinitis Pigmentosa (RP) in its earliest stages. As a preventative measure, the nervous system can be shielded from harm by administering neuroprotective substances like antioxidants, anti-apoptotic drugs, and neurotropic substances like ciliaryneurotrophic factors (CNTF) [42,43, 45], brain-derived neurotrophic factors, and fibroblast growth factors [44]. According to current understanding, neuroprotective substances function by preventing apoptosis and inflammatory processes, as well as by lowering oxidative stress and free radicals [45]. Since it has been clinically demonstrated to do so, CNTF is currently mostly utilized to halt retinal degeneration [46, 47, 48].

Conclusions:-

A genetic disease called retinitis pigmentosa (RP) affects the retina and promotes progressive visual loss. The present article has briefly covered the classification, epidemiology, clinical symptoms, and prognosis of RP. Conventional RP treatments, such as vitamin A supplements, sun protection, visual aids, and surgical procedures, have slowed the disease's course and lessened its symptoms, but they do not target the hereditary basis of the condition. People with RP now have new hope thanks to recent medicinal developments including gene therapy like voretigeneneparvovec (Luxterna) for RPE65. These treatments try to treat the disease's basic genetic cause and have the potential to arrest the course of RP, providing some patients with a cure. But before they can be used in clinical settings, the majority of other gene therapy targets are still in the preclinical stages of research.

Stem cell treatment, optogenetics, and neuroprotective drugs are some of the additional preclinical therapeutic modalities on the horizon in addition to gene therapy. These have demonstrated encouraging outcomes in human models and offer the possibility of undoing the harm, regaining vision, and completely altering the way RP is treated. It could be challenging to diagnose and treat retinitis pigmentosa. We can open new doors to cutting-edge drugs that will transform how we address RP and provide hope for those who are afflicted with the condition due to advancements in our understanding of its molecular evidence in support.

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