**Chapter XX**

**Emerging Drug Therapies for Inherited Retinal Dystrophies**

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**Abstract**

Worldwide, 1 in 2000 people suffer from inherited retinal dystrophies (IRD). Individuals with IRD typically present with progressive vision loss that ultimately results in blindness. Unfortunately, effective treatment options are not widely available due to the genetic and clinical heterogeneity of these diseases. There are multiple gene, cell and drug-based therapies in various phases of clinical trials for IRD. This mini-review documents current progress made in drug-based clinical trials for treating IRD.

**Abbreviations**

FDA: US Food and Drug Administration

IRD: Inherited Retinal Dystrophies

LCA: Leber congenital amaurosis

RP: Retinitis Pigmentosa

SD: Stargardt’s disease

**XX.1 Inherited Retinal Dystrophies**

The prevalence of inherited retinal dystrophies (IRD) is 1 in 2000 people worldwide (Cremers et al. 2018). IRD are classified as rare diseases by the World Health Organization and common examples are retinitis pigmentosa (RP), cone-rod dystrophies, Leber congenital amaurosis (LCA), Stargardt’s disease (SD) and macular degenerations (Veleri et al. 2015). Broadly, IRD are characterized by degeneration of retinal rod and cone photoreceptors, which consequently lead to blindness. Current research efforts for identification of treatments include stem cells, gene therapy, small molecule drugs, and light sensitive prostheses, the vast majority of which are not approved, but in preclinical-clinical trials (Duncan et al. 2018; Oner 2018). This review focuses on progress with drug-based therapies in clinical trial for IRD.

**XX.2 Drug Therapies in Clinical Trials**

**Neuroprotectants**

***Neurotropic factors***

Neurotrophins are a family of growth factors regulating development, differentiation and survival of neuronal cells (Huang and Reichardt 2001). A Phase I/II (NCT02110225) and a Phase II (NCT02609165), have been conducted to assess the safety and efficacy of recombinant human nerve growth factor (rhNGF) eye drops in 50 patients with RP and 45 patients with RP associated cystoid macular oedema (RP-CME), respectively. Both studies are completed but did not report any results. Levodopa (L-DOPA) controls the release of neurotropic factors beneficial in neurodegenerative diseases (Sarkar et al. 2016). In a retrospective study, L-DOPA delayed age-related macular degeneration development, signifying potential benefits for IRD (Brilliant et al. 2016). Currently a Phase II trial (NCT02837640) is recruiting 50 RP patients to determine the effect of L-DOPA on visual function.

Alpha-2 (α2) adrenoceptor agonists display strong neuroprotective potential in animal models (Sacchetti et al. 2015). A trial with 26 IRD patients, did not find significant differences in visual acuity, color vision, and contrast sensitivity following Brimonidine tartrate, a selective α2-adrenoceptor agonist treatment (Merin et al. 2008). A 12-month Phase I/II (NCT00661479) clinical trial showed modest changes in best corrected visual acuity and contrast sensitivity after 6 months in 21 RP patients, with two participants presenting adverse events (syncope and myelitis).

***Epigenetic Modulators***

Histone deacetylase inhibitors (HDACi) are gaining attention as a therapeutic option for IRD. Preclinical studies prove HDACi can efficiently restore visual function and neuroprotect photoreceptors (Daly et al. 2017; Leyk et al. 2017; Vent-Schmidt et al. 2017; Trifunovic et al. 2018). A small-scale Phase I trial using valproic acid (VPA), significantly improved visual fields with mild/tolerated side effects in RP patients (Clemson et al. 2011). Subsequent studies reported either detrimental or no benefit from VPA treatment of RP patients (Sisk 2012; Bhalla et al. 2013; Totan et al. 2017). In a pilot study, 29 patients took VPA for 6 months, reported short-term benefits and improvement in visual field which were reversed upon treatment termination (Iraha et al. 2016). A Phase II trial (NCT01233609) conducted with 90 autosomal dominant RP (adRP) patients, reported VPA treatment for a year, lead to deterioration of visual field (Birch et al. 2018). A larger scale Phase II trial (NCT01399515) with 200 participants concluded in 2016, though the study results are not published.

***Cannabinoids***

Medical cannabis produces pain alleviating and neuroprotective effects in neurodegenerative diseases, cancer, multiple sclerosis and epilepsy (Sun et al. 2015). In an adRP rat model, synthetic cannabinoid HU-210 preserved retinal function and reduced photoreceptor loss (Lax et al. 2014). In diabetic retinopathy, cannabidiol treatment halted retinal cell death and significantly reduced oxidative stress (El-Remessy et al. 2006). A Phase I clinical trial (NCT03078309) is currently recruiting. The study aim is to determine the effects of cannabis derivatives on visual function in healthy and RP patients.

**Visual Cycle Modulators**

Visual cycle deficits can result in IRD, as a consequence of either inadequate production of 11-cis retinal), or build-up of excess toxic retinoid cycle by-products (Ward et al. 2018). *RPE65* and *LRAT*, key members of the visual cycle, are implicated in RP and LCA (Hussain et al. 2018). RPE65 and LRAT regulate 11-cis retinal and rhodopsin, deficiencies in which, causes retinal degeneration (Redmond et al. 1998). Clinical trials (NCT01521793, NCT01014052) are investigating the effects of QLT091001, 9-cis-retinyl-acetate, which can bypass visual cycle dysfunction, in RP and LCA patients with *RPE65* or *LRAT* mutations. Phase Ib clinical trials show improved visual function (Scholl et al. 2015). Some adverse effects include moderate to severe headaches and photophobia (Koenekoop et al. 2014). NCT01543906 a Phase I trial completed in 2014 with oral QLT091001, assessed visual function improvements in five adRP patients with *RPE65* mutations, results are not reported to date.

9-cis-retinal administration to *Rpe65* mutant mice significantly improved visual function, postulating that conversion of 9-cis-β-carotene-rich to 9-cis-retinal in the retina, could likewise improve vision (Van Hooser et al. 2000). *Dunaliella* capsules, are over-the-counter supplement composed of 9-cis-β-carotene-rich powder. A Phase I trial (NCT01256697) completed by 29 RP patients treated daily with *alga Dunaliella bardawil* reported some patients to have non-significant increased response to light (Rotenstreich et al. 2013). Current trials underway involve larger patient groups, longer treatment duration and are at Phase II/III (NCT01680510) or Phase I/II (NCT02018692). Thus far, adverse side effects are not reported.

Emixustat, is a small, non-retinoid derivative of retinylamine that inhibits RPE65, preventing A2E formation, due to a decrease in 11-cis retinol production (Bavik et al. 2015). SD arises from mutations in the visual cycle *ABCA4* gene which accumulate toxic vitamin A by-products. Preclinical mouse models of autosomal recessive SD show Emixustat treatment significantly reduces A2E levels and has received orphan drug designation from the FDA (Zhang et al. 2015). Thirty patients completed a Phase IIa clinical trial (NCT03033108) in December 2017, with results pending. *ALK-001* (C20-D3-retinyl acetate) is a modified form of vitamin A which reduces abnormal vitamin A dimerization (Kaufman et al. 2011). Currently, a Phase II trial (NCT02402660) is under development for SD patients (Sears et al. 2017).

**Anti-inflammatory**

Anti-inflammatory drugs have entered clinical trials for vision loss related to RP-CME, and ocular diseases associated with autoimmunity (Strong et al. 2017). A Phase II study (NCT02804360) of intravitreal dexamethasone implant (IVDI) in 34 RP-CME patients showed improved visual acuity, decreased central macular thickness, and increased intraocular pressure. Improved visual acuity was transient in ~50% of patients and CME recurrence necessitated repeat injections. A long-lasting treatment effect was observed in 14 eyes following multiple injections, but seven of them developed cataracts (Mansour et al. 2018).

Overactive complement is implicated in SD (Lenis et al. 2017). Zimura inhibits the complement system by inhibiting complement protein C5. A Phase II trial (NCT03364153) is assessing intravitreal administrated Zimura in 120 patients with autosomal recessive SD. Phase I/II clinical trial (NCT02140164) evaluated oral minocycline, an inhibitor of microglial activation, for RP. Minocycline might help prevent/reduce inflammation; however, five of seven participants completed the 12-month study, showed a non-significant reduction in CME. Adverse events included hypothyroidism and reduced visual acuity.

Fluocinolone acetonide (FA) is a synthetic hydrocortisone derivative. Intravitreal infusion of FA reduces retinal inflammation, preserves retinal structure and function in rodent models of photoreceptor degeneration (Glybina et al. 2010). A pilot study is investigating intravitreal FA over a 36-month period in patients with RP (EudraCT Number: 2016-002523-28).

**Anti-oxidants**

Oxidative damage is a major contributor to photoreceptor death in patients with RP (Campochiaro and Mir 2018). N-acetyl cysteine (NAC) is protective against oxidative stress by increasing intracellular glutathione levels (Mokhtari et al. 2017). NAC promotes cone survival in preclinical models of RP and inhibits the TNFα-NF/kB pro-inflammatory axis (Oka et al. 2000; Lee et al. 2011). A Phase I trial in 30 RP patients (NCT03063021) is underway.

**XX.3 Conclusion**

Many current drugs in trial are repurposed or target secondary pathologies. While there is rationale for this selection, focusing on this subset leaves a huge untapped chemical space. One unbiased opportunity, is phenotype-based screening (Szabo et al. 2017) wherein drugs are tested directly against a pathological phenotype rather than a target *e.g.* drugs restore vision *in vivo,* reduce oxidative stress in cell lines or reduce cell death in *ex vivo* eyecups (Chen et al. 2017; Daly et al. 2017; Sher et al. 2018). A drawback can be that the effector target needs to be determined separately. However, this target agnostic approach implicitly results in the discovery of novel drugs, therapeutic targets and mechanisms of disease.

There are limited therapeutic options for IRD. Most clinical trials have yet to report study outcomes. The lack of transparency in reporting outcome of clinical trials makes it impossible to critically evaluate the efficacy and market potential of said drugs. Additionally, given the clinical and genetic heterogeneity of IRD, the observed disparities across different trials for the same drug, stipulates the importance to selectively identify patient cohorts who stand to benefit most from the treatment strategy.

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