Emerging drugs for the treatment of Glaucoma

Khanna J[1], Katyal D[2]*

[1]SeniorResident, Department of Pharmacology, Pt. B.D. Sharma PGIMS, Rohtak, Haryana

[2]Medical Officer, Jhajjar, Haryana

*Corresponding Author's E-mail: jk.jyotikhanna1@gmail.com

ABSTRACT

Glaucoma is a slowly progressive degenerative disorder of optic nerve caused by increased intraocular pressure and vascular derangement. This is the second leading cause of blindness worldwide. The drugs currently available to treat glaucoma are β blockers, prostaglandin analogue, alpha-agonists, carbonic anhydrase inhibitors and cholinergic agonists. None of the available drugs can reverse or arrest neuronal loss. Moreover, usually single therapies are not effective in most of the cases and combination therapies are needed. The adverse effects noted with the currently used medications in glaucoma include as dry eye, burning, stinging sensations, tearing and allergic reactions. The goal of research in this field is to arrest/reverse apoptotic damage to optic nerve and hence slow the disease progression and improve quality of life. This article discusses some of the newer drug options which seem to be promising in the treatment of glaucoma and are in one or the other stage of clinical development.

Keywords:Glaucoma, Emerging drugs.

Access this article online	
Quick Response Code:	www.oijms.org.in

INTRODUCTION

Glaucoma is not a single disease process but a group of disorders characterized by a progressive optic neuropathy resulting in a characteristic appearance of the optic disc and a specific pattern of irreversible visual field defects that are associated frequently but not invariably with raised intraocular pressure (IOP).[1]It is the second leading cause of irreversible blindness worldwide. It is largely a disease of the ageing eye.Prevalence of glaucoma is increasing worldwide, due to longer life expectancy. [2]

It is estimated that there are more than 60 million cases of glaucoma worldwide and it will increase to 80 million by 2020.[3] It is estimated that more than 3 million people are blind due to glaucoma.[4]The estimated prevalence of glaucoma is 2.65% in people above 40 years of age. Globally, primary open-angle glaucoma (POAG) is more prevalent than primary angle closure glaucoma (PACG) and responsible for around three fourth of all glaucoma cases.[4] In India, the estimated number of cases of glaucoma is 12 million, around one fifth of the global burden of glaucoma.[3]

There are several types of glaucoma like congenital glaucoma, primary glaucoma (Open angle and closed angle) and secondary glaucoma (lens dislocation, phacolysis, trauma,

uveitis, topical corticosteroids). The two main types are open angle glaucoma and angle closure glaucoma.[5]Various risk factors for glaucoma development are age (more commonly seen in elderly between 5th and 7th decades), race(more common, develops earlier and is more severe in black), myopes, diabetics, cigarette smoking, topical corticosteroids.[6]

Glaucomatous optic neuropathy is a chronic process, which progresses over many years.[7]The primary mechanism of retinal ganglion cell damage in glaucoma is not completely understood. Elevated IOP (>21 mmHg) and vascular insufficiency are the primary factors which result in various secondary factors like growth factor deprivation, glutamate receptor upregulation, oxidative stress, nitric oxide synthatase activation, TNF alpha receptor upregulation and extracellular matrix changes leading to retinal ganglion cell apoptosis.[8] The proposed mechanisms for RGC death includes mechanical compression due to raised intraocular pressure, excitotoxicity (glutamate, oxygen free radicals, or nitric oxidewhich are released when RGCs undergo death due to primary insults), failure of auto-regulatory mechanism of blood flow to retina & optic nerve, neurotropic growth factor deprivation.[7]

Current treatment options can be broadly classified as drugs which decrease aqueous production and drugs which increase aqueous outflow. Drugs which decrease aqueous production includes beta-blockers (levobunolol, timolol, betaxolol), alpha-2 adrenergic Agonists (apraclonidine, brimonidine), carbonic anhydrase inhibitors (acetazolamide, dorzolamide) and drugs which increase aqueous outflow includes nonspecific adrenergic agonists (epinephrine, dipivefrine), parasympathomimetics (pilocarpine, carbachol, echothiophate) and prostaglandins (latanoprost).[9]

Despite the available treatment options, glaucoma remains the second leading cause of irreversible blindness worldwide. Once optic neuropathy and RGC loss are established, no currently available treatment can reverse the process. Also, many of the currently available topical medications are associated with various adverse effectssuch as dry eye, burning, stinging sensations, tearing and allergic reactions.

Novel compounds in drug classes of FDA standards-

The efficacy standard for new IOP-lowering agents is equivalent to one of four FDA approved ophthalmic drugs: timolol maleate, latanoprost, bimatoprost, or travoprost.

Novel drug targeting β-receptors

SYL-040012 (Bamosiran) is a small interfering RNA (siRNA) agent, that triggers RNA interference (RNAi), an endogenous cellular process in which double-stranded RNA can cause physiological gene silencing in organisms.[10] SYL-040012 reduces IOP by knockdown of β_2-adrenergic receptors.[11] The efficacy of this agent is equivalent to timolol and is the only novel compound that targets β-receptors.

This new pharmacological approach appears to be promising for glaucoma treatment; however RNAi-based drugs face potential development obstacles such as targeted delivery, efficacy,

selectivity, and safety.[12-14]It is currently in phase II clinical trial.[15]

Novel prostanoid EP2 receptor Agonist

PF-04217329 (Taprenepag isopropyl) is a novel prostanoid EP_2 receptor agonist. It is believed to act by increasing uveoscleral outflow. Its activity at dose levels (0.0025%, 0.01% and 0.02%) is comparable and additive to already available prostanoid analogue, latanoprost (0.005%). It is currently in Phase II clinical trials.[16]

AR-102 (mopidamol)-FP agonist and NCX-116/BOL-303259-X/PF-03187207 (nitric oxide donating prostaglandin $F_{2\alpha}$ agonist) are some other molecules in phase II clinical trial for glaucoma.[11]

NOVEL TARGETS

Latrunculins

Latrunculins are macrolides that inhibit actin polymerization by sequestering monomeric actin in trabecular meshwork and thereby increases trabecular outflow by a novel mechanism of actin cytoskeleton disruption in cells of the conventional pathway.[17]It is currently in phase I trials. By far, results of the study are insignificant. At dose levels of 0.02% and 0.05%, side effects reported are mild ocular redness, irritation, and transient increase in central corneal thickness.[18]

Rho-associated protein kinase and norepineprine transporter

The Rho family of small guanosinetriphosphatases (GTPases) has a central role in cellular processes like actin cytoskeleton assembly, actin-myosin mediated cell contraction, cell shape, motility, proliferation and apoptosis.[19] ROCK (Rho-associated coiled coil-forming protein kinase) is an effector molecule of Rho in the Rho-dependent signal transduction pathway and cause polymerazition of actin molecules. Thus, specific inhibitors of ROCK that modulate changes in the actin cytoskeleton and cellular motility of the trabecular meshwork, Schlemm's canal, and ciliary muscle may comprise a potential new class of ocular hypotensive drugs that enhance aqueous drainage.[20] Inhibition of norepineprine transporter (NET) is known to increase adrenergic signaling and appears to be responsible for the decrease in aqueous humor production.[21] AR-13324, K-115, Y-39983, RKI-983, AMA-0076, AR-13533 are some of the molecules which are under clinical development for the effective and safe treatment of glaucoma.

Topical AR-13324 (Rhopressa) is a Rho kinase/norepinephrine transporter (ROCK/NET) inhibitor.[22] Acting via these targets, the drug reduces intraocular pressure (IOP) by three mechanisms i) through ROCK inhibition, it increases fluid outflow through the trabecular meshwork (TM) which accounts for approximately 80% of fluid drainage from the eye; (ii) as demonstrated in a preclinical study, it reduces episcleral venous pressure (EVP) which represents the pressure of the blood in the episcleral veins of the eye where aqueous fluid drains into the bloodstream; and (iii) through NET inhibition, it reduces the production of aqueous fluid.[23,24] Given as a once-daily eye drop (0.02%) for a period of

28 days,it has shown to significantly reduces IOP by three mechanisms in eyes with ocular hypertension or open-angle glaucoma in phase II clinical trials. The study showed that the lowering of IOP by AR-13324 was non-inferior to latanoprost.[22]The most common adverse event reported with its use in phase II clinical trials is hyperemia. The incidence of this adverse effect decrease as the study progressed. There was no systemic side effect reported during a period of 28 days once daily topical eye treatment with this drug.[22]This molecule is currently in Phase III clinical trial for the treatment of glaucoma.[25]

Topical PG-324 (Roclatan) is a fixed dose combination of AR-13324 (Rhopressa;0.02%) and latanoprost (0.005%).[26] It has quadruple mechanism of action to lower IOP and only glaucoma product that covers the full spectrum of currently known IOP-lowering MOAs. Three mechanisms are similar to AR-13324 and the fourth mechanism is of latanoprost i.e. lowering of IOP by increasing the uveoscleral outflow. The side effect reported was mild hyperemia. No systemic side effect was noted.[27]It is currently in Phase III clinical trial.[28]

AMA 0076, a ROCK inhibitor, applied as eye drops, effectively penetrates the cornea, and produces its therapeutic effect by increasing the outflow of aqueous humor through the trabecular meshwork, thereby reducing IOP. Systemically, AMA0076 is rapidly converted into an inactive form which is eliminated from the body. This unique feature is aimed at preventing off-target activity. Hyperemia which is a common side effect of ROCK inhibitors leading to patient non-compliance is not seen with this drug.[29]This drug is presently in phase II clinical trial for glaucoma.[30]

K-115 (Ripasudil; 0.04%), another ROCK inhibitor, has completed Phase III study produced significant, dose-dependent reductions in IOP in eyes with glaucoma and ocular hypertension. The effects were additive when combined with current prostaglandin agent or β–blocker. The new drug produced tolerable side effects mostly limited to transient hyperemia.[31]

Adenosine receptor

Adenosine is an endogenous purine nucleoside that modulates physiological and pathophysiological processes by activating the G protein-coupled adenosine receptors.[32] A3 adenosine receptor (A3AR) agonists have been found to protect normal cells from apoptosis via the downregulation of death signals.[33]

CF101, an A3 adenosine receptor (A3AR) agonist, is a novel, first in class small molecule orally bioavailable drug which binds with high affinity and selectivity to the A3AR, which is known to be over-expressed in inflammatory cells. The drug acts as a neuro-protective agent and prevents apoptosis of retinal ganglion cells. The drug has excellent safety profile and anti-inflammatory effects.[34]It is presently in phase II clinical trial.[35]

INO-8875 (Trabodenoson) is a selective adenosine-1 receptor agonist, under development for the treatment of arrhythmia and glaucoma. It is currently in phase II

clinical trial for glaucoma and ocular hypertension.[36]

NMDA receptor antagonists

NMDA antagonist provides neuroprotection by blocking increase in glutamate, excess of which is responsible for excitotoxicity (cell death) by facilitating calcium entry into a cell. Memantine, an N-methyl-D-aspartate subtype glutamate receptor antagonist is in the phase III clinical trial for glaucoma.[37] However, two phase III trial for the safety and efficacy of memantine failed to show statistical significance for the primary endpoints. [38]

Some other NMDA receptor antagonists in clinical trials are:
Eliprodil: It is a non-competitive NMDA antagonist; providing protection from glutamate mediated cytotoxicity to retinal ganglion cells. It has been shown to be neuroprotective in cultured neurons of brain and retina from excitotoxic and ischemia damage at doses of 1-10mg/kg.[39] Eliprodil is a racemic compound and R-enantiomer of Eliprodil rather than the S-enantiomer is effective in preserving retinal ganglion cells from injury and therefore can be of major use in glaucoma.[40] Clinical trials of this drug in humans have not been started yet.

Complementary and alternative Medicine

Froskolin

Forskolin is a chemical found in the roots of the plant Plectranthusbarbatus (Coleus forskohlii).[41] Applied as 1% eyedrop it has shown to decrease aqueous outflow and hence, decrease IOP in patients of glaucoma with concomitant asthma where β blockers are contraindicated. In the study it has shown to be effective at concentration as low as 0.15%. The drug has fast onset of action (1hour), action peaks at 2 hours and remained significant for at least 5 hours. The adverse events reported were mild and transient in nature and included redness, burning and itching.[42]

CONCLUSION

Glaucoma is a serious disease of eye that can cause blindness if not treated early. None of the currently available medications can reverse/arrest progression of the disease. Many emerging therapies are directed at reversing the disease progression but still ideal medication for this is not yet available. Further researches with newer targets or newer drugs acting on known targets are required to achieve the goal of maximum benefit at minimal risks.

REFERENCES

1. EyeWorld: Diseases Of The Eye And Treatment: Glaucoma. [Internet]. 2010.[updated 2010 Dec 30; cited 2015 Aug 3]. Available from: ikeyes.blogspot.com/2010/12/glaucoma-definition-and-aetiology.htm
2. Glaucoma is second leading cause of blindness globally. Bulletin of the World Health Organization | November 2004, 82 (11)
3. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020.Br J Ophthalmol 2006;90:262-7
4. Pascolini D, Mariotti SP. Global estimates of visual impairment:

2010. Br J Ophthalmol 2012;96:614-8
5. Types of glaucoma. Glaucoma research foundation. [Internet] .2015 [updated 2015 Jul 14; cited 2015 Aug 3] Available from: www.glaucoma.org/glaucoma/types-of-glaucoma.php.
6. Primary open angle glaucoma. Eye World: Diseases of the eye and treatment. [Internet]. 2010 [updated 2010 Dec 29; cited 2015 Aug 3] Available from: ikeyes.blogspot.com/2010/12/primary-open-angle-glaucoma.html.
7. Agarwal R, Gupta SK, Agarwal P, Saxena R, and Agrawal SS. Current concepts in the pathophysiology of glaucoma. Indian J Ophthalmol. 2009 Jul-Aug; 57(4): 257–266.
8. Pinar S and Vecino E. Current Trends in Glaucoma: What about Neuroprotection? In: Westerhouse AN. Eye Research Developments. Nova Science Publishers, Inc.2009. Available from: Research Gate
9. Basic and clinical science course. Glaucoma. American Academy of Ophthalmology. [Internet]. 2011-12. Available from: ISBN 978-1615251179.
10. Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in Caenorhabditiselegans. Nature. 1998;391(6669):806–811.
11. Chen J, Runyan S A, Robinson MR. Novel ocular antihypertensive compounds in clinical trials. Clinical Ophthalmology 2011:5 667–677. Available from: www.dovepress.com
12. Qiu S, Adema CM, Lane T. A computational study of off-target effects of RNA interference. Nucleic Acids Res. 2005;33(6):1834–1847.
13. Castanotto D, Rossi JJ. The promises and pitfalls of RNA-interferencebased therapeutics. Nature. 2009;457(7228):426–433.
14. Wang J, Lu Z, Wientjes MG, Au JL. Delivery of siRNA therapeutics: barriers and carriers. AAPS J. 2010;12(4):492–503.
15. SYL040012 treatment for open angle glaucoma (SYLTAG).[Internet]. 2014 [updated: 2014 Dec 4; cited: 2015 Aug 3]. Available from: https://clinicaltrials.gov/ct2/show/NCT02250612.
16. Schachar RA1, Raber S, Courtney R, Zhang M. A phase 2, randomized, dose-response trial of taprenepag isopropyl (PF-04217329) versus latanoprost 0.005% in open-angle glaucoma and ocular hypertension. Curr Eye Res. 2011 Sep;36(9):809-1.
17. Peterson JA, Tian B, McLaren JW, Hubbard WC, Geiger B, KaufmanPL. Latrunculins' effects on intraocular pressure, aqueous humor flow, and corneal endothelium. Investigative Ophthalmology & Visual Science.2000.41(7),1749–58.
18. Ritch R, Schiewe M, Zink RC et al. Latrunculin (INS115644) reduces intraocular pressure (IOP) in ocular hypertension OHT) and primary open angle glaucoma (POAG). Investigative Ophthalmology & Visual Science, vol. 51, ARVO E- Abstract and Poster 6432, 2010.
19. Riento K, Ridley AJ. Rocks: multifunctional kinases in cell behaviour. Nat Rev Mol Cell Biol. 2003;4(6):446–456.

20. Nakajima E, Nakajima T, Minagawa Y, Shearer TR, Azuma M. 48. Contribution of ROCK in contraction of trabecular meshwork: proposed mechanism for regulating aqueous outflow in monkey and human eyes. J Pharm Sci 2005; 94: 701-8.
21. Serle JB and Kopczynsk CC. The quest for a trabecular outflow drug. Opthalmology times. [Internet]. 2014 [updated 2014 Jan 15; cited 2015 Aug 3]. Available from: http://ophthalmologytimes.modernmedicine.com/ophthalmologytimes.
22. Krader CG, Bacharach J. First-in-class glaucoma therapy shows promise in phase II study: Rho kinase/norepinephrine transport inhibitor (0.02%) was non-inferior to latanoprost. Opthalmology times. [Internet]. 2015 [updated 2015 Feb 1; cited 2015 Aug 12]. Available from: http://ophthalmologytimes.modernmedicine.com/ophthalmologytimes/news.
23. Wang RF, Williamson JE, Kopczynski C, Serle JB. Effect of 0.04% AR-13324, a ROCK, and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. J Glaucoma 2015. 24(1):51-4.
24. Kiel JW, Kopczynski C. Effect of AR-13324 on episcleral venous pressure (EVP) in Dutch Belted rabbits. ARVO 2014. Abstract 2900.
25. A Double-masked Study of AR-13324 in Patients With Glaucoma and Ocular Hypertension (Rocket-2). [Internet]. 2014 [updated 2014 Jul 31; cited 2015 AUG 3]. Available from: https://clinicaltrials.gov/ct2/show/NCT02207621.
26. Krader, Guttman C. Fixed Dose of ROCK/NET Inhibitor, Latanoprost Meets Efficacy Endpoint.Ophthalmology Times. [Internet] 2014 [updated 2014 Aug 1; cited 2015 Aug 3]. Available from: http://www.highbeam.com/doc/1P3-3410964251.html.
27. Aerie Pharmaceuticals Reports Roclatan Phase 2b Results Achieve All Clinical Endpoints. [Internet]. 2014 [updated 2014 Jun 25; cited 2015 Aug 4]. Available from: http://investors.aeriepharma.com/releasedetail.cfm?ReleaseID=856396.
28. A Phase 3 Study of PG324 Ophthalmic Solution (Roclatan) in Patients with Elevated Intraocular Pressure. [Internet]. 2015 [updated 2015 May 7; cited 2015 Aug 4]. Available from: adisinsight.springer.com/trials/700247686.
29. AMA0076 for Glaucoma. Amakem therapeutics. [Internet]. 2014 [updated 2014; cited 2015 Aug 4]. Available from: http://www.amakem.com/ama0076-for-glaucoma.
30. Amakem Initiates Phase 2 Dose-Ranging Study for Locally-Acting ROCK Inhibitor AMA0076 in Glaucoma. [Internet]. 2014 [updated 2014 May 13; cited 2015 Aug 4]. Available from: http://www.amakem.com/news/95/169.
31. Henahan S. ROCK inhibitors may provide benefits beyond IOP lowering. New glaucoma drugs . Euro times. [Internet] .2014 [updated 2014 Sep;

cited 2015 Aug 5]. Available from: http://www.eurotimes.org/node/1455.

32. Chen J, Runyan SA, Robinson MR, "Novel ocular antihypertensive compounds in clinical trials," Clinical Ophthalmology, vol. 5, no. 1, pp. 667–677, 2011.
33. Fishman P1, Cohen S, Bar-Yehuda S. Targeting the A3 adenosine receptor for glaucoma treatment.Mol Med Rep. 2013 Jun;7(6):1723-5. doi: 10.3892/mmr.2013.1413. Epub 2013 Apr 4.
34. OphthaliX Signs Term Sheet to Acquire Improved Vision Systems Ltd. [Internet]. 2015 [updated 2015 May 4; cited 2015 Aug 4]. Available at: http://www.prnewswire.com/news-releases.
35. Second part of the glaucoma phase II study has been approved in a European Country. [Internet] 2014 [updated 2014 Dec 15; cited 2015 Aug 4]. Available from: http://www.prnewswire.com/news-releases.
36. Drug profile. Trabodenoson. [Internet] 2015 [updated 2015 Aug 11; cited 2015 Aug 13]. Available at: http://adisinsight.springer.com/drugs/800019882.
37. Memantine in patients with chronic glaucoma. [Internet]. 2010 [updated 2010 Nov 3; cited 2015 Aug 4]. Available from: https://clinicaltrials.gov/ct2/show/NCT00168350.
38. Wheeler LA, Gil DW, woldemussie E. Role of alpha-2 77. Adrenergic receptors in neuroprotection and glaucoma. SurvOphthalmol 2001; 45 (Suppl 3): S290-4.
39. Kapin M, D Oshi R, Scatton B, Desantis LM, Chandler ML. Neuroprotective effects of Eliprodil in retina excitotoxicity and ischemia. Invest Opthalmolvissci 1999;40:1177-82.
40. R-eliprodil for treating glaucoma. [Internet]. [updated 2001; cited 2015 Aug 4] Available at:http://www.google.com/patents/WO2001085152A2?cl=en
41. Forskolin: Uses, Side Effects, Interactions and Warnings. [Internet]. Available from: http://www.webmd.com/vitamins-supplements/ingredientmono-1044-forskolin.aspx?activeingredientid=1044&activeingredientname=forskolin
42. Majeed M, Nagabhushanam K, Natarajan S, Vaidyanathan P, Karri SK, Josea JA. Efficacy and safety of 1% forskolin eye drops in open angle glaucoma – An open label study. Saudi J Ophthalmol. 2015 Jul-Sep; 29(3): 197–200.