

A new futuristic glaucoma therapeutic management paradigm

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ABSTRACT

Glaucoma is a group of diseases, characterized by a progressive form of optic nerve damage. Current studies indicate more selective pathophysiological involvement, thereby targeted therapies are warranted. Although both the prostaglandin analogs and beta blockers are still, most commonly used drugs for glaucoma, due to their efficacy, lack of adverse effects. In addition, a stepped care approach is the corner stone for its management. In addition, attempts have been made to enhance patient compliance and ocular delivery of already available anti-glaucoma drugs such as pilocarpine and timolol maleate. Notable among futuristic treatment options are; novel delivery systems, benzalkonium chloride-free drugs, various glaucoma drainage devices, new targeted therapies and prompt diagnosis plus aggressive treatment, in patients with primary angle closure glaucoma. Promising new focus on vision sparing, greater patient safety and tolerability will provide improved treatment options and long-term preservation of vision and quality of life.

Keywords: Novel delivery systems, Benzalkonium chloride-free drugs, Glaucoma drainage devices, New targeted therapies

INTRODUCTION

Glaucoma continues to be a major cause of irreversible visual disability all over the world. Current studies indicate that the involvement of excitatory and inhibitory neurotransmitters, namely, glutamate, gamma amino butyric acid and glycine is particularly linked to glaucoma. Apoptosis or genetically programmed cell death has also been implicated as a mechanism for progression of glaucoma.

There has been a dramatic change in the approach to medical therapy of glaucoma during the previous two decades. Until the 1980s, miotics were the drugs of first choice for treating this disease but at present beta blockers are regarded as the

first choice drugs. Apart from beta blockers, a number of newer drugs are now been in use. These are latanoprost, travoprost, apraclonidine, dorzolamide, and brimonidine, etc.

In addition, attempts have been made to enhance patient compliance and ocular delivery of already available drugs such as pilocarpine and timolol maleate. Notable among the delivery systems are electronic devices, ocular inserts, liposomes, nanospheres, contact lenses, sophisticated surgical implants, etc. Use of viscoelastic vehicles (soluble polymers to soluble gels) in ophthalmic formulations, soluble ophthalmic drugs inserts benzalkonium chloride (BKC-free drugs) and nano solution drugs, etc. have been

made to enhance patient compliance. Finally, an effort has been made, on the use of glaucoma drainage devices and on an update on emergency treatment for acute angle-closure glaucoma (ACG).

FUTURISTIC TREATMENT OPTIONS

Novel delivery systems¹

- a. Liposomes and nanospheres: recently, pilocarpine has been encapsulated in liposomes and delivered in solution as an eye drop. This would reduce dosing of pilocarpine from 4 times daily to twice daily. The nanocapsules, consisting of a diblock copolymer with a hydrophilic component and a hydrophobic block are releasing their drug load very quickly. This strategy of providing the drug with a carrier that allows it, to stay longer on the surface of the cornea, is an effective approach to reduce dosing frequency
- b. Contact lenses as delivery vehicles: soft contact lenses, consisting of polymers of N, N-diethylacrylamide and methacrylic acid, have been shown to deliver timolol for longer periods
- c. Sophisticated surgical implants: one novel approach is to implant a reservoir system in the subconjunctival space. The micro electromechanical system uses electrolysis to create bubbles that push the drug out of the reservoir of the device, which has a port that allows multiple loading of the drugs
- d. Injectable systems: it is possible to develop a long-term release i.e. 3-4 months, formulation of a glaucoma medication that can be injected in an office setting. Subconjunctival administration of glaucoma medications in extended-release formulations can avoid patient adherence issue. Sustained delivery of drugs from degradable polyesters has been studied for subconjunctival administration, including antibiotics after cataract surgery, carboplatin for murine retinoblastoma, and celecoxib to reduce oxidative stress, etc.²

BKC-free drugs

As per guidelines, latanoprost is used as the first-line treatment for glaucoma. Currently, marketed latanoprost contains a preservative, BKC, which not only acts as a preservative but also solubilizes the drug in its micellar structure. Furthermore, on long-term such BKC-containing eye drops may be harmful to the eye surface; and are not stable at room temperatures.

A BKC-free latanoprost (SPARC), intended for improved retention in the eye, has completed a Phase III clinical trial in India. This is a non-infringing formulation, has many advantages. Furthermore, the removal of BKC reduce tearing, burning, itching, and hence reduces drainage from the surface of the eye. It contains latanoprost in an unbound

form, which also enables its partition across eye tissues and does not need any special refrigeration for storage/transport.³

Glaucoma drainage devices

Are designed to divert aqueous humor from the anterior chamber to an external reservoir, where a fibrous capsule forms about 4-6 weeks after surgery and regulates the flow. These devices have shown success in controlling IOT in eyes with previously failed trabeculectomy and in eyes with insufficient conjunctiva because of scarring from prior surgical procedures or injuries. They also have demonstrated success in complicated glaucomas such as uveitic glaucoma, neovascular glaucoma, pediatric glaucoma, previously failed trabeculectomy and much difficult glaucomas. Since, their introduction, numerous modifications in design and improvements in surgical technique have enhanced clinical outcomes and minimized complications.⁴ These devices are available in different sizes, materials and design. The decision to choose a particular type of drainage device depends on a patient's underlying characteristics in terms of pre-operative intraocular pressure (IOP), optic nerve status, desired long-term IOP control, and the surgeon's comfort and preference. Different devices are; valved implants, non-valved implants and molteno implants. Finally, careful preoperative screening and planning along with meticulous surgical techniques help to minimize post-operative complications,⁵ is required.

New therapies

With the host of new therapies that are on the horizon, it's a good time to pursue the pipeline. Various recent/new treatment options are:

- a. IOP lowering agents: they are highly effective at reducing IOP via an enhancement of aqueous humor outflow through the uveo scleral space. Besides all those established drugs (Table 1), a list of new IOP - lowering agents including LM7101, (a limkinase 2 inhibitor), adenosine R1 agonist INO-8875, are under development
- b. New delivery systems: depot forms of effective drugs such as the travoprost punctal plugs are currently in clinical trials. Another delivery vehicle is a variant of the contact lens, is designed to reside under the lid rather than on the cornea
- c. IOP - monitoring devices: diurnal variations of IOP have been thought to play an important role in the progression of the disease. Recent approach uses implantable micro sensors that transmit pressure data to a handheld external device and others is the iSense, is in the development. An alternative technology employs a contact lens with an embedded strain gauge, to record continuous 24-hrs changes in ocular surface tension
- d. IOP - lowering devices: the Hydrus Microstent is designed to act much like a cardiac stent, it is placed in

- the canal of Schlemm and maintains a patent canal that can mediate aqueous drainage
- e. Targeting neuroprotection: a growing body of evidence suggests that many of drugs that are used to treat elevated IOP, also have neuroprotective effects. Synthesis of cytokines and growth factors for reactive astrocytes and altered expression of cell surface adhesion molecules including neural cell adhesion molecule, hold promise.⁶

Recent approach for emergency treatment for ACG

Targeted treatment options include:

- a. Medical (pharmaceutical) options: various topical, oral and systemic agents are indicated depending on the severity (Table 1)

I. Topical	
•	Prostaglandin analogues e.g. latanoprost, travoprost
•	Beta blockers e.g. timolol, betaxolol
•	Alpha ₂ agonists, such as brimonidine, apraclonidine
•	Topical carbonic anhydrase inhibitor (CAI) such as dorzolamide and brinzolamide
•	Dipivefrine, adrenaline
•	Combination of drugs (beta blockers +1-2 drugs from other groups).
II. Systemic	
•	Systemic CAI such as acetazolamide before going for surgery
•	Surgery-laser/incisional.

- b. Corneal indentation: it is an adjunct procedure in which a cotton tipped applicator, or gonioscopy lens is used to intend the central cornea. Repeated indentation each time lasting approximately 30 sec followed by 30 sec rest, over 10-15 mins displaces aqueous peripherally into the angle and opens the angle mechanically.
- c. Laser treatment: in recent years the use of lasers has already replaced surgical iridectomy as the procedure of choice in most cases of ACG. Types of laser treatment used are: laser peripheral iridotomies (LPIs) and laser peripheral gonioplasty.
- d. Surgery: when the acute ACG attack cannot be broken within 3-6 hrs of initiating treatment and laser gonioplasty has been unsuccessful, the patient requires surgical iridectomy. Other situations in which surgical

iridectomy may be required are: when LPIs close repeatedly, when laser is unavailable, when patients are uncooperative or has severe nystagmus, etc.⁷

CONSLUSION

The wide variety of topically effective anti-glaucoma drugs, novel delivery systems, BKC-free drugs, glaucoma drainage devices, etc. are available today. A lot many, are in the developmental stages, represent a significant advancement in the ocular therapeutics. The presentation of primary ACG varies greatly, a prompt diagnosis and aggressive management are necessary. A “new futuristic glaucoma therapeutic management paradigm” where clinical success is no longer simply measured by achieved level of IOP but also by long-term preservation of visual function and patient’s quality of life, is expected/required.

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