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Combination Therapy in Glaucoma Treatment

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Commentary

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Glaucoma, an optic neuropathy, is a worldwide leading cause of visual impairment and blindness [1]. It is a neurodegenerative disease involving the loss of Retinal Ganglion Cells (RGC) and Raised Intraocular Pressure (IOP) is the leading and only mutable risk factor for glaucoma [2].

Control of IOP with a minimum complications or side effects remains the mainstay therapy for the first-line treatment of glaucoma [3]. Most of the antiglaucomatic drugs make it possible to control IOP in many glaucoma patients with a once-daily dose of a single agent. The preferred medication is topical monotherapy, but it is associated with several limitations. In some cases use of single agent was not able to control IOP effectively and also monotherapy has the potential to lose its effectiveness overtime [4]. There may be several mechanisms for loss of the effectiveness of these monotherapeutic agents; some include tachyphylaxis and disease progression [4]. This loss may be resolved by using combination of different classes of drugs which aims at different targets or pathways to combat the disease with minimal adverse effects [5]. The combination therapy could also improve tolerability because two compounds may be employed below their individual dose thresholds [6]. The term "combination" refers all the ways in which one drug may be added to another. This may be achieved by combining two monotherapeutic agents in one dosage form known as fixed dose or fixed combination, or the two therapeutic agents can be instilled simultaneously but separately (unfixed combination).

Use of a fixed combination rather than two different formulations can result in enhanced patient's compliance as it simplifies the medical regimen and reduces the number of instillations per day [7,8]. Improved compliance may result in better IOP control, and using a fixed combination may lower the exposure to preservatives and prevent the washout effect, as well [9]. Lower copayments along with insurance to buy the drugs may benefit the patient economically. Additionally, theuse of fixed combinations primarily facilitates adherence and persistence with treatment [1]. Adherence is an important concern in glaucoma because up to 80% of patients may not take their medication as prescribed [1]. A drawback of fixed combination therapy that can be emphasized is that as both the drugs are combined into one formulation, it is not possible to change the drug concentration or dosing schedule for one component medication independently of the other. But, if adherence is improved by simplifying the dosing regimen, advantages of using a fixed combination therapy outweigh this drawback [10].

Commonly used classes of IOP-lowering medications are alpha adrenergic receptor agonists (alpha agonists), beta-adrenergic receptor antagonists (beta-blockers), Carbonic Anhydrase Inhibitors (CAIs), and prostaglandin analogs. In recent years, there is a substantial increase in the use of fixed combinations of IOP-lowering drugs for treatment of glaucoma. Some of the fixed combinations that are currently available for lowering the IOP contain timolol and either CAI dorzolamide or alpha agonist brimonidine or prostaglandin analog, and the examples include Cosopt^{*}(timolol/dorzolamide), Combigan^{*} (timolol/brimonidine), Xalacom^{*} (timolol/latanoprost), Duotrav^{*} (timolol/travoprost), Ganfort^{*} (timolol/bimatoprost). The results from the clinical studies indicated that fixed combination was more therapeutically effective than individual therapeutic agentsalone in lowering IOP [6]. Fixed combinations provide a better option for patients who need more than one drug to control IOP, and hence they can be considered as important adjuncts to the armamentarium of available therapies for treating glaucoma.

Lowering the IOP remains the clinician's principal medication therapy; this treatment is often only partly effective. Despite of IOP lowering therapy, in some subset of patient's glaucoma continues to worsen [11-13]. As glaucoma is a multifactorial, chronic degenerative optic neuropathy characterized structurally by a loss of RGC and optic nerve axons, IOP lowering treatment alone is not fully effective and it is unable to prevent progressive vision loss in some glaucoma patients. The final stage in glaucoma involves RGC damage and death [13]. This damage was observed at statistically high, average, or low levels of IOP. This necessitates an alternative treatment paradigm to manage this problem more efficiently, which can be achieved by considering neuroprotection approach. Neuroprotection approach attempts to stimulate or impede specific biochemical pathways that may prevent neuronal injury or promote neuronal recovery and protect the RGC from glaucomatous insults.

Neuroprotective agents help to prevent the loss of RGCs and degeneration of optic nerve fibers independently of the particular factors that damage the optic nerve. Till date, there are no neuroprotective drugs that have been approved by the FDA. For these reasons, there isa considerable amount of research going on for the development of neuroprotective agents that can reduce the rate of glaucoma progression [14,15]. Different neuroprotective agents that are in consideration include neurotropic factors, N-methyl-D-aspartate (NMDA) receptor antagonists, anti-apoptotic agents, nitric oxide synthase antagonists, antioxidants, calcium channel blockers, and gene therapy [15]. Though there are several theoretically effective neuroprotective therapies but unfortunately they remained somewhat limited in practice. Several pharmacologically active neuroprotective agents which showed great potential in the laboratory have almost invariably failed in the process of translation to clinic [14-16]. The current challenge for researchers in this field is to identify clinically effective neuroprotective agents.

Although IOP lowering is the current mainstay treatment for glaucoma, the demand for additional non-IOP-lowering therapies that are directed at preventing further glaucomatous progression has gained much interest from the patients, physicians and researchers. Therefore, a more realistic ideal combination therapy would be one that can lower IOP and also attenuates RGC death with minimal adverse effects. Extensive research in this field will unquestionably lead us forward into the promising era of glaucoma therapy.

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