Rescula as an Alternative Therapy for Beta-blockers with Long-term Drift Effect in Glaucoma Patients

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The purpose of this study was to evaluate both the intraocular pressure (IOP)-decreasing and neuroprotective effects of Rescula (0.12% unoprostone isopropyl) as an alternative therapy to beta-blockers with a long-term drift effect in patients with glaucoma. Twenty-eight patients with unilateral or bilateral glaucoma were treated with Rescula instead of the original beta-blocker therapy. IOP was measured using a Goldmann applanation tonometer, and visual field defects were evaluated quantitatively by Humphrey automatic perimetry central 30-2 threshold test. The mean follow-up time was at least 1 year. Rescula achieved a significant (p = 0.00001) and long-lasting reduction in IOP (from 20.78 ± 2.71 to 17.14 ± 2.70 mmHg) in patients with open-angle glaucoma after 12 months of follow-up. It also demonstrated a significant (p = 0.02) IOP-reducing effect (from 20.67 ± 3.60 to 16.36 ± 3.67 mmHg) in patients with angle-closure glaucoma 12 months later. The mean deviation of visual field defects changed from –13.27 dB baseline to –10.64 dB at 12 months as evaluated by Humphrey field analyzer II central 30-2 threshold test after Rescula; however, there was no statistical difference (p = 0.098). Our results showed that Rescula has a significant IOP-reducing effect as an alternative therapy to beta-blockers with long-term drift effect in patients with open-angle and angle-closure glaucoma. However, a neuroprotective effect to prevent further progression of the visual field defect in patients with glaucoma was not demonstrated in this study.

Key Words: glaucoma, Rescula, intraocular pressure, visual field
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Glaucoma is a disease characterized by the combination of damage to the optic nerve and loss of visual field, primarily due to the death of retinal ganglion cells and gradual cupping of the optic nerve head [1]. Elevated intraocular pressure (IOP) is not only a main characteristic of glaucomatous disease, but also a significant etiologic factor. Although the exact etiology of glaucoma has not been completely understood, vascular factors that decrease ocular blood flow and result in subsequent dysfunction of neuroprotection are considered to be important factors in the development of the disease [2–6]. Since glaucoma is a multifaceted disease, there is significant research in process to develop the regimens that not only lower IOP, but also address other physiologic aspects of the disease, particularly in neuroprotective and vascular dysfunction.

Current treatment strategies for glaucoma and ocular hypertension (OHT) are primarily aimed at decreasing elevated IOP. Topical beta-blockers are usually the first line of ocular hypotensive therapy. If target IOP is not reached after a period of monotherapy, switching treatment is used to obtain the desired IOP-decreasing effect, especially switching to drugs with different mechanisms [7].

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Unoprostone isopropyl is a docosanoid derived from a metabolite of a primary prostaglandin, 13,14-dihydro-15-ketoprostaglandin. It was found to have a significant IOP-lowering effect and was as effective as timolol in reducing IOP in primary open-angle glaucoma (POAG) [8,9]. It acts by increasing uveoscleral outflow in a similar manner to latanoprost [10,11]. Although the adjunctive use of unoprostone has a significant added IOP-decreasing effect in patients with POAG or OHT treated with beta-blockers alone, we used unoprostone alone (unoprostone isopropyl 0.12%, Rescula) as a replacement, not as adjunctive therapy, to evaluate its long-term efficacy and safety.

In this study, we collected topical beta-blocker-treated glaucoma patients with so-called long-term drift effect. Long-term drift is a phenomenon that occurs in patients with extended use of beta-blockers. There is a slow, but real upward "drift" in IOP, as the response to beta receptors is affected by constant exposure to an agonist. We evaluated the IOP-lowering effect and visual field preservation of Rescula as monotherapy to substitute beta-blockers with long-term drift effect in glaucoma patients.

Patients and Methods

This study was prospectively carried out at the Kaohsiung Medical University Hospital, Taiwan. All patients enrolled in the study were followed in a glaucoma clinic and treated initially with beta-blockers, including 0.5% Bunolgan (levobunolol), 0.5% Timoptol XE (timolol), and 2% Arteoptic (carteolol) for at least 1 year. The types of glaucoma in these patients included POAG, chronic angle-closure glaucoma (CACG), normal tension glaucoma (NTG), and OHT. The reasons why beta-blockers were discontinued included elevated IOP (> 21 mmHg) with mild-to-moderate visual field loss (mean deviation of visual field defect between –3 and –25 dB) and progressive visual field defect with normal IOP (≤ 21 mmHg). Patients received an alternative therapy with Rescula (unoprostone 0.12%) and were consecutively collected at the glaucoma clinic. Rescula was used twice a day, at 8 a.m. and 8 p.m., with the same frequency as beta-blockers. Baseline IOP was defined at the time when beta blockers were stopped. To prevent irreversible damage to the patients, we switched the eye drops without a washout period. Instead, we ignored the IOPs within the first month when two kinds of eye drops were overlapping. After switching to Rescula, IOPs were collected during the 1st, 3rd, 6th and 12th months. IOPs were measured thrice for each eye at the same time, and they were measured at different times, at 9 a.m., 1 p.m. and 5 p.m., on the same day for correction of diurnal changes. The IOPs of each time point of visiting were averaged. Visual field defects were determined by the Humphrey automatic perimetry central 30-2 threshold test. The mean deviations were collected before Rescula treatment and after using Rescula for 6, 12 and 24 months.

Statistical analysis

Statistical comparison of IOP reduction and visual field defect was performed by Student's paired *t* test.

Results

Patient demographics

A total of 28 patients were enrolled in this study; 30 eyes of 17 patients were open-angle glaucoma (12 POAG, 3 OHT, 2 NTG), 15 eyes of 10 patients were angle-closure glaucoma, and both eyes of one patient had a combination of open-angle and angle-closure glaucoma. There were 6 male and 11 female patients in the open-angle glaucoma group, and 6 male and 4 female patients in the angle-closure glaucoma group. The mean age of the patients in the open-angle glaucoma group (48.71 ± 14.85 years) was younger than that in the angle-closure glaucoma group (65.1 ± 6.24 years) (Table 1).

Efficacy in lowering intraocular pressure

In the present study, changes in IOP in the right eyes of all patients decreased significantly ($p = 0.013$) after shifting to Rescula, from 21.31 ± 3.17 to 17.90 ± 1.89 mmHg; in the left eyes, IOP decreased significantly ($p = 0.025$) from 20.30 ± 2.63 to 17.53 ± 3.19 mmHg. Since the IOP decreases were significant in both right and left eyes, we used all the IOP values of the patients who were divided into the two subgroups — open-angle and angle-closure glaucoma. Rescula showed a significant ($p = 0.00001$) and long-lasting IOP-lowering effect (from 20.78 ± 2.71 to 17.14 ± 2.70 mmHg) in patients with open-angle glaucoma after 12 months' follow-up. It also demonstrated a significant ($p = 0.02$) IOP-reducing effect (from 20.67 ± 3.60 to 16.36 ± 3.67 mmHg) in patients with angle-closure glaucoma after 12 months' follow-up. Changes in IOP during the study periods are presented in Table 2.

Changes in visual field defect

The mean deviation of visual field defect changed from –13.27 dB (baseline) to –10.64 dB (12 months after treatment with Rescula). There was no significant difference in the visual field defect ($p = 0.098$).

Table 1. Characteristics of the glaucoma patients

Type of glaucoma	Open angle			Angle-closure	Combined
	POAG	OHT	NTG		
No. of patients (eyes)	12 (21)	3 (5)	2 (4)	10 (15)	1 (2)
Sex (male/female)		6/11		6/4	1/0
Mean age (yr)		48.71 ± 14.85		65.1 ± 6.24	66
Bilateral/unilateral		13/4		5/5	1/0

POAG = primary open-angle glaucoma; OHT = ocular hypertension; NTG = normal tension glaucoma.

Table 2. Intraocular pressure before and after Rescula treatment

	Open-angle glaucoma	*p*	Angle-closure glaucoma	*p*
Before Rescula (mmHg)	20.78 ± 2.71		20.67 ± 3.60	
After Rescula (mmHg)				
4 wk	19.09 ± 3.49	0.0007	17.50 ± 3.68	0.003
12 wk	18.86 ± 2.36	0.0037	17.00 ± 3.58	0.02
24 wk	18.87 ± 4.15	0.0047	16.26 ± 3.00	0.01
48 wk	17.14 ± 2.70	0.00001	16.36 ± 3.67	0.02

Discussion

Rescula (unoprostone isopropyl) is generally prescribed to patients with open-angle glaucoma. In our study, Rescula was prescribed not only to patients with open-angle glaucoma, but also to patients with angle-closure glaucoma. The results revealed that Rescula is effective in both open-angle ($p = 0.00001$) and angle-closure glaucoma ($p = 0.02$) after 12 months' follow-up.

In general, beta-blockers have an excellent IOP-decreasing effect and are commonly used as the first-line IOP-lowering agent. Rescula is usually used as an adjunctive therapy to beta-blockers, but not as a replacement therapy. There were two reasons for using Rescula both as monotherapy and as a replacement of beta-blockers instead of adjunctive therapy. First, all our patients had used beta-blockers for at least 1 year. Initially, the IOP-lowering effect was good; however, IOP elevated gradually due to the long-term drift effect. In this situation, changing the eye drops or adding a second eye drop to lower IOP might be the next step. It was decided to stop the beta-blockers. Second, glaucoma is a chronic disease and requires long-term use of hypotensive medication. Thus, patient compliance is one of the major factors affecting long-term prognosis. The more convenient and simple the medication, the better is the compliance of patients. Monotherapy is still the best choice. As an alternative therapy, prostaglandin analog is usually the first choice of treatment. Although other prostaglandin analogs such as latanoprost may have better IOP-lowering effects than Rescula, Rescula has few of the local cosmetic side effects (such as conjunctival congestion and permanent melanin pigmentation of the eyelids and iris) that patients are seriously concerned about. Thus, Rescula was chosen as the alternative agent and the patients remained on monotherapy at the same frequency to observe if IOP would decrease as expected. The results revealed that Rescula can lower IOP effectively after switching from beta-blockers.

Unoprostone may have a neuroprotective effect because it can counteract endothelin-1-induced vasoconstriction in both animal and human models [12–14], increase ocular blood flow and blood flow velocity in rabbits and humans [12,15–18], and protect against ischemia and photoreceptor damage in rats [19–21], as well as against glutamate-mediated neuronal death in an *in vitro* model [22]. We evaluated the changes of visual field defect before and after Rescula treatment to ascertain whether Rescula can work as a preserver of the visual field. The results revealed a minimal improvement in visual field defect, but there was no significant difference ($p = 0.098$). Since visual field defect is generally irreversible, the preservation of visual defect after 12 months' follow-up in this study may suggest that

Rescula might have a neuroprotective effect to prevent its further progression. Unfortunately, due to the fact that there was no control group in this study, it is not possible to conclude whether or not Rescula can preserve the visual field and prevent further progression of the visual field defect either by its IOP-decreasing effect or other neuroprotective effects. Further study is warranted.

Conclusion

Rescula (0.12% unoprostone isopropyl) had significant ($p < 0.001$) and long-lasting IOP-lowering effects in patients with open-angle glaucoma in this study. Rescula also had a significant ($p = 0.02$) IOP-reducing effect in patients with angle-closure glaucoma. We suggest that Rescula can provide an IOP-reducing effect as an alternative therapy to beta-blockers in patients with open-angle glaucoma and angle-closure glaucoma who suffer from the long-term drift effect as a result of beta-blocker use.

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以 Rescula 取代漸失效的 Beta-blockers 來治療青光眼之成效 — 原著

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以 Rescula (0.12% unoprostone isopropyl) 取代 beta-blockers 來治療青光眼病患，評估 Rescula 對於降低眼壓的效果以及保護視神經 (視野的維持或改善) 的成效。在本研究中的 28 位青光眼病人，原本是以 beta-blockers 長期治療青光眼，因降壓效果減弱或視野缺損持續惡化，而改以 Rescula 取代來治療青光眼。眼壓的測量是以 Goldmann 平壓式眼壓計來做測量而視野的缺損則是以 Humphrey 自動視野儀程式 30-2 來定量評估。每位患者至少追蹤一年以上。Rescula 使用在隅角開放型青光眼患者之後，有顯著的降壓效果 ($p < 0.00001$ 從 20.78 ± 2.71 降至 17.14 ± 2.70 mmHg)；此外，對於隅角閉鎖型的青光眼患者，同樣也有顯著的降壓效果 ($p = 0.02$ 從 20.67 ± 3.60 降至 16.36 ± 3.67 mmHg)。而視野的平均缺損在 Rescula 使用前後，雖然無統計學上有意義的差別，也從使用前平均缺損 −13.27 dB 減少到使用後一年的 −10.64 dB。我們的結果顯示以 Rescula 取代漸失效的 beta-blockers 來治療隅角開放型及隅角閉鎖型的青光眼患者，都能夠提供良好的降壓效果；另外從視野的變化，本研究無法證明 Rescula 具有神經保護的功能，能夠避免病人的視野繼續喪失。

關鍵詞：Rescula，青光眼，眼壓，視野

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