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# Long-term intraocular pressure after switching a combination ophthalmic medication of $\beta$ -blocker/prostaglandin

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## Abstract:

**PURPOSE:** We examined intraocular pressure (IOP)-reducing effects 12 months after switching timolol maleate/travoprost combination ophthalmic solution in one bottle (TM/TR-COMBI-SOL) to carteolol hydrochloride/latanoprost combination ophthalmic solution in one bottle (CR/LT-COMBI-SOL).

**CASES:** The participants included 25 patients (25 eyes) who could be followed up for 12 months after a switch from TM/TR-COMBI-SOL to CR/LT-COMBI-SOL in Saiseikai Arida Hospital between March 1, 2017, and August 31, 2018. They consisted of patients in whom antiglaucoma eye drop other than TM/TR-COMBI-SOL had not been used (monotherapy group, 12 patients [12 eyes],  $12.8 \pm 3.0$  mmHg) and those in whom antiglaucoma eye drop other than TM/TR-COMBI-SOL had been concomitantly used (multitherapy group, 13 patients [13 eyes],  $13.8 \pm 2.4$  mmHg). We excluded patients in whom drugs for glaucoma were changed or added during the follow-up and those who underwent intraocular surgery.

**MATERIALS AND METHODS:** We retrospectively and statistically examined the IOP before eye drop switching and after 1, 6, and 12 months, using the paired *t*-test.

**RESULTS:** The IOPs 1 month after eye drop switching in the monotherapy group and multitherapy group were  $12.5 \pm 3.3$  and  $13.8 \pm 2.5$  mmHg, respectively. The values after 6 months were  $13.5 \pm 3.0$  and  $11.5 \pm 2.7$  mmHg, respectively. Those after 12 months were  $12.8 \pm 2.7$  and  $11.7 \pm 2.5$  mmHg, respectively. In the monotherapy group, there was no significant difference during the follow-up period. In the multitherapy group, there were significant decreases in comparison with the preswitching value after 6 and 12 months ( $P < 0.05$ , respectively).

**CONCLUSION:** The IOP-reducing effects of CR/LT-COMBI-SOL were similar to those of TM/TR-COMBI-SOL. However, the effects may be enhanced after switching from TM/TR-COMBI-SOL in patients receiving multitherapy.

## Keywords:

Antiglaucoma combination ophthalmic solution, carteolol hydrochloride, intraocular pressure-reducing effect

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## Introduction

Glaucoma is a chronic disease, requiring long-term continuous treatment. Evidence-based treatment is ocular pressure-reducing therapy,<sup>[1,2]</sup> and eye drop treatment is important regardless of the stage. As first-choice drugs, prostaglandin (PG) analog and  $\beta$ -blockers are frequently selected due to

potent intraocular pressure (IOP)-reducing effects, but ocular pressure control with a single drug alone is often impossible. For this reason, the development and sales of combination ophthalmic solutions have recently been promoted to avoid unfavorable adherence related to treatment with several eye drop preparations.

As of February 2019, timolol maleate, as a  $\beta$ -blocker, is contained in all PG/ $\beta$ -blocker

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combination ophthalmic solutions in one bottle. In Japan, PG/ $\beta$ -blocker combination ophthalmic solution in one bottle containing carteolol hydrochloride, Mikeluna<sup>®</sup> (carteolol hydrochloride and latanoprost-containing ophthalmic solution, Otsuka Pharmaceutical Co., Ltd., CR/LT COMBI SOL), became commercially available in January 2017, although it has not been commercially available in the world market. Timolol maleate exhibits anesthetic actions on the ocular surface and may cause corneal epithelium disorder.<sup>[3-6]</sup>

We previously reported (in Japanese) that switching to Mikeluna<sup>®</sup> significantly alleviated corneal epithelium disorder within 3 months in patients treated with timolol maleate/travoprost combination ophthalmic solution in one bottle, DuoTrav<sup>®</sup> (Alcon Inc., TM/TR COMBI SOL), which may cause corneal epithelium disorder, and that the IOP-reducing effects were similar in a short period (1–3 months after switching).<sup>[7]</sup> However, it is necessary to examine the long-term IOP-reducing effects of CR/LT COMBI SOL, which are important for glaucoma treatment. No study has reported the long-term course.

In this study, we investigated IOP-reducing effects for 12 months after a switch from conventional PG/ $\beta$ -blocker combination ophthalmic solution, TM/TR COMBI SOL, to CR/LT COMBI SOL.

## Subjects

Of patients treated with antiglaucoma ophthalmic solution containing TM/TR COMBI SOL in Saiseikai Arida Hospital (Yuasa-cho, Arida-gun, Wakayama Prefecture, Japan) between March 1, 2017, and August 31, 2018, the participants included 25 patients (25 eyes) (13 males, 12 females,  $73.4 \pm 7.6$  years old) who could be followed up for 12 months after a switch from TM/TR COMBI SOL to CR/LT COMBI SOL.

The mean IOP was  $13.5 \pm 2.7$  mmHg, and the logarithmic visual acuity was  $0.27 \pm 0.58$ . Of patients in whom antiglaucoma ophthalmic solution other than TM/TR COMBI SOL had been concomitantly used and those in whom it was changed or discontinued after switching to CR/LT COMBI SOL were excluded from the study. Furthermore, those in whom ophthalmic solution for dry eye treatment or antiallergic ophthalmic solution was added or discontinued during the study period were included. Patients who underwent ophthalmological surgery were excluded. In those in whom the bilateral eyes were to be included, the left eye was investigated.

The above 25 patients (25 eyes) involving the presence or absence of combination therapy with antiglaucoma eye drop other than TM/TR COMBI SOL were regarded as the participants overall.

We defined the patients treated with only TM/TR COMBI SOL as “monotherapy group” and using TM/TR COMBI SOL and any other antiglaucoma eyedrops as “multitherapy group.” Monotherapy group was 12 patients (12 eyes), and multitherapy group was 13 patients (13 eyes).

Monotherapy group consisted of 4 males and 8 females, with a mean age of  $72.6 \pm 5.5$  years. The mean IOP was  $12.8 \pm 3.0$  mmHg, and the logarithmic visual acuity was  $0.05 \pm 0.17$ . Multitherapy group consisted of 9 males and 4 females, with a mean age of  $74.1 \pm 9.0$  years. The mean IOP was  $13.8 \pm 2.4$  mmHg, and the logarithmic visual acuity was  $0.47 \pm 0.71$ . Multitherapy group had been combined with dorzolamide hydrochloride in 4 patients, ripasudil hydrochloride hydrate in 4, and brimonidine tartrate in all 13, including duplicated patients.

## Methods

In the participants overall, monotherapy group, and multitherapy group, we statistically examined the IOP before TM/TR COMBI SOL switching to CR/LT COMBI SOL and after 1, 3, 6, 8, 10, and 12 months using the paired *t*-test.

The rate of change in the ocular pressure in comparison with the preswitching value 1, 3, and 6 months after switching was compared between the monotherapy and multitherapy groups. The participants were divided into those with a  $\geq 20\%$  decrease in the IOP, those with a  $\pm < 20\%$  change, and those with a  $\geq 20\%$  increase.

All patients were measured IOP from 9 am to 12 am.

This was a retrospective study, and its protocol was approved by the Ethics Review Board of Saiseikai Arida Hospital (Approval no. 0037).

## Results

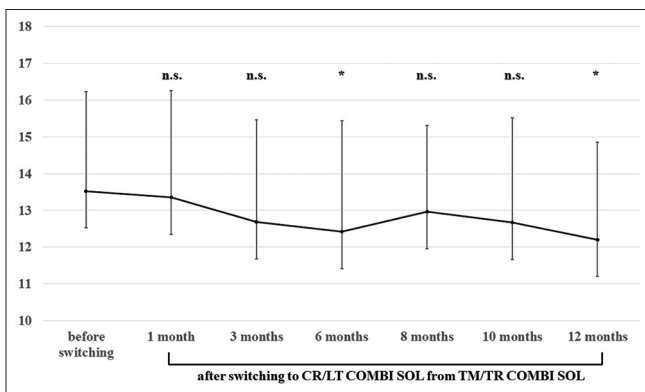
In the participants overall, the mean IOP 1, 3, 6, 8, 10, and 12 months after switching to CR/LT were  $13.3 \pm 2.9$  ( $P = 1.000$ ),  $12.7 \pm 2.8$  ( $P = 0.234$ ),  $12.3 \pm 3.0$  ( $P = 0.042$ ),  $13.0 \pm 2.4$  ( $P = 0.251$ ),  $12.7 \pm 2.9$  ( $P = 0.168$ ), and  $12.2 \pm 2.6$  ( $P = 0.016$ ) mmHg, respectively [Figure 1]. There were significant decreases in the ocular pressure in comparison with the preswitching value 6 and 12 months after switching to CR/LT ( $P < 0.05$  each). There was no significant switching-related change in the IOP at any other point ( $P > 0.05$  each).

In the monotherapy group, the mean ocular pressures 1, 3, 6, 8, 10, and 12 months after switching to CR/LT COMBI SOL were  $12.5 \pm 3.3$  ( $P = 0.858$ ),  $13.1 \pm 2.8$  ( $P = 0.480$ ),  $13.5 \pm 3.0$  ( $P = 0.223$ ),  $13.4 \pm 2.2$  ( $P = 0.322$ ),  $13.1 \pm 2.4$

( $P = 0.601$ ), and  $12.8 \pm 2.7$  ( $P = 1.000$ ) mmHg, respectively [Figure 2]. There was no significant switching-related change in the IOP at any point ( $P > 0.05$  on all measurement points).

In this group, patients with a  $\geq 20\%$  decrease in the IOP 1, 3, and 6 months after switching to CR/LT COMBI SOL accounted for 0, 8.3, and 8.3%, respectively. Those with a  $\pm < 20\%$  change accounted for 100, 83.3, and 66.7%, respectively. Those with a  $\geq 20\%$  increase accounted for 0, 8.3, and 25.0%, respectively [Figure 3].

In the multitherapy group, the mean IOP 1, 3, 6, 8, 10, and 12 months after switching to CR/LT COMBI SOL were  $13.8 \pm 2.5$  ( $P = 0.713$ ),  $12.1 \pm 2.7$  ( $P = 0.036$ ),  $11.4 \pm 2.7$  ( $P = 0.001$ ),  $12.2 \pm 2.4$  ( $P = 0.014$ ),  $12.0 \pm 3.1$  ( $P = 0.054$ ), and  $11.7 \pm 2.5$  mmHg ( $P = 0.018$ ), respectively [Figure 4]. There were significant decreases in the IOP in comparison with the preswitching value 3, 6, 8, and 12 months after switching to CR/LT COMBI SOL (after 3, 8, and 12 months:  $P < 0.05$  each, after 6 months:  $P < 0.01$ ).



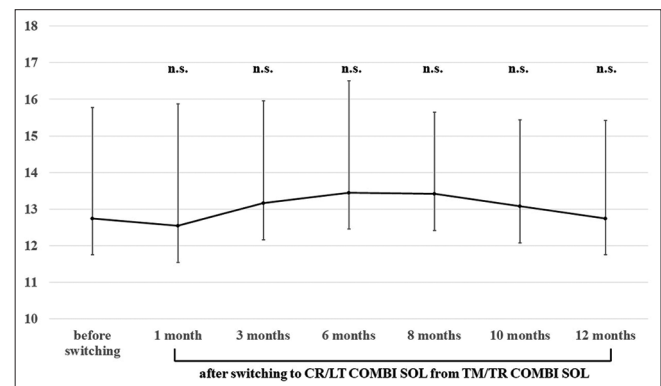
**Figure 1:** Progress of intraocular pressure after switching to carteolol hydrochloride/latanoprost combination ophthalmic solution in one bottle from timolol maleate/travoprost combination ophthalmic solution in one bottle (the subjects overall). Vertical axis = IOP (mmHg), Horizontal axis = each point to measure IOP, n. s. = not significant, \* =  $P < 0.05$

When examining changes in the IOP individually in this group, patients with a  $\geq 20\%$  decrease in the IOP in comparison with the preswitching value 1, 3, and 6 months after switching to CR/LT COMBI SOL accounted for 0, 33.3, and 46.2%, respectively. Those with a  $\pm < 20\%$  change accounted for 100, 66.7, and 53.8%, respectively. There was no patient with a  $\geq 20\%$  increase at any point [Figure 3].

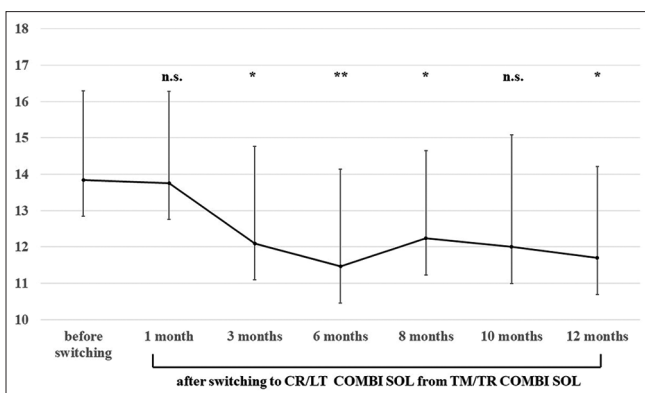
## Discussion

CR/LT COMBI SOL is carteolol hydrochloride/latanoprost combination ophthalmic solution in one bottle, being the only PG/ $\beta$ -blocker combination ophthalmic solution in one bottle containing carteolol hydrochloride that is commercially available as of July 2018.

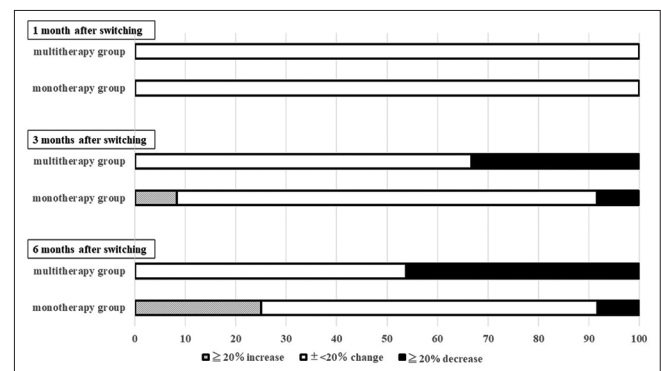
In this study, we examined the IOP-reducing effects of PG/ $\beta$ -blocker combination ophthalmic solution in one bottle switching. CR/LT COMBI SOL contains latanoprost as a PG analog, and TM/TR COMBI SOL contains travoprost. The former contains carteolol



**Figure 2:** Progress of intraocular pressure after switching to carteolol hydrochloride/latanoprost combination ophthalmic solution in one bottle from timolol maleate/travoprost combination ophthalmic solution in one bottle (monotherapy group). Vertical axis = IOP (mmHg), Horizontal axis = each point to measure IOP, n. s. = not significant



**Figure 3:** The rate of change in the ocular pressure in comparison with the preswitching value. Upper row = 1 month after switching eye drop, Middle row = 3 months after switching eye drop, Lower row = 6 months after switching eye drop, Horizontal axis = the rate of each status (%)



**Figure 4:** Progress of intraocular pressure after switching to carteolol hydrochloride/latanoprost combination ophthalmic solution in one bottle from timolol maleate/travoprost combination ophthalmic solution in one bottle (multitherapy group). Vertical axis = IOP (mmHg), Horizontal axis = each point to measure IOP, n. s. = not significant, \* =  $P < 0.05$ , \*\* =  $P < 0.01$

hydrochloride as a  $\beta$ -blocker, and the latter contains timolol maleate. Several studies indicated that the IOP-reducing effects of latanoprost were similar to those of travoprost,<sup>[8]</sup> and that the IOP-reducing effects of carteolol hydrochloride were similar to those of timolol maleate.<sup>[9,10]</sup> We previously reported that there was no significant difference in the IOP-reducing effects between CR/LT COMBI SOL and TM/TR COMBI SOL in a short period (1–3 months) in patients with corneal epithelial disorder, suggesting that the IOP-reducing effects of the two preparations as combination ophthalmic solution in one bottle are similar despite different PG/ $\beta$ -blocker combinations.<sup>[7]</sup>

The results of this study showed that there were significant decreases in the IOP in comparison with the preswitching value 6 and 12 months after a switch from TM/TR COMBI SOL to CR/LT COMBI SOL in the participants overall. This switch significantly reduced the IOP as mid-to-long-term effects. We investigated these effects by dividing the participants into two groups based on the presence or absence of the concomitant use of antiglaucoma ophthalmic solution other than TM/TR COMBI SOL.

In the monotherapy group, there was no significant change in the ocular pressure related to switching to CR/LT COMBI SOL at any measurement point, suggesting that the IOP-reducing effects of TM/TR COMBI SOL are similar to those of CR/LT COMBI SOL. The IOP-reducing effects of PGs and  $\beta$ -blockers contained in the respective combination solutions may have been similar, respectively, as previously reported.

However, the IOP-reducing effects were enhanced  $\geq 3$  months after switching to CR/LT COMBI SOL in patients in whom PG/ $\beta$ -blocker combination ophthalmic solution had been combined with other types of antiglaucoma eye drop. The IOP was also lower than the preswitching value 12 months after switching.

Furthermore, to examine the timing of evaluating IOP-reducing effects after a switch from TM/TR COMBI SOL to CR/LT COMBI SOL, the participants were divided into those with a  $\geq 20\%$  increase in the IOP after ophthalmic solution switching, those with a  $\geq 20\%$  decrease, and those with a  $\pm < 20\%$  change. At 1 month, the rate of change was  $< 20\%$  in comparison with the preswitching value in all patients regardless of the presence or absence of antiglaucoma eye drop other than PG/ $\beta$ -blocker combination ophthalmic solution. However, at 3 months, some patients showed a  $\geq 20\%$  increase or decrease [Figure 3]. This suggests that IOP-reducing effects should be reassessed  $\geq 3$  months after switching to CR/LT COMBI SOL.

As the reason, changes in eye drop adherence and IOP-reducing effects related to combination therapy with antiglaucoma eye drop may have improved adherence after switching to CR/LT COMBI SOL in comparison with that during TM/TR COMBI SOL therapy. In the future, the eye drop switching-related sense of use or eye drop adherence must be additionally investigated through a questionnaire survey involving patients.

Concerning the IOP-reducing effects of combination therapy with antiglaucoma eye drop, brimonidine tartrate had been used in all patients receiving such combination therapy. Brimonidine tartrate is not frequently selected as a first-choice drug, but in the future, it may be necessary to further examine the IOP-reducing effects of TM/TR COMBI SOL or CR/LT COMBI SOL additionally prescribed in patients receiving brimonidine tartrate in large-scale or blind studies.

Case numbers in this study were relatively small; therefore, we need a large-scale study or blind studies to confirm these results in the future.

## Conclusion

Although the case numbers were relatively small, the results suggest that the IOP-reducing effects of TM/TR COMBI SOL are similar to those of CR/LT COMBI SOL. However, switching to CR/LT COMBI SOL may further decrease the IOP in patients receiving multitherapy with TM/TR COMBI SOL and other antiglaucoma eye drop.

IOP-reducing effects should be assessed  $\geq 3$  months after a switch from TM/TR COMBI SOL to CR/LT COMBI SOL regardless of the presence or absence of concomitantly prescribed antiglaucoma eye drop.

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Nil.

## Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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