GLAUCOMA

Intraocular pressure-lowering efficacy and ocular safety of Rho-kinase inhibitor in glaucoma: a meta-analysis and systematic review of prospective randomized trials

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Abstract

Purpose To evaluate the intraocular pressure (IOP)-reducing efficacy and safety of Rho-kinase inhibitor (RKI).

Methods Published studies in PubMed and EMBASE were searched on March 20, 2021. Study selection and data extraction were performed according to PRISMA. Meta-analysis of the IOP-lowering effect was performed with the bivariate random-effects model, with studies categorized into 2 classes: RKI versus placebo and RKI versus another medication. The main outcome was the difference in IOP reduction between RKI and non-RKI groups. Subgroup analysis of adjunctive RKI efficacy and additional review of its major ocular adverse events (AE) were also performed.

Results Ten (2.6%) out of 391 studies were retrieved. In the RKI versus placebo class, RKI showed greater IOP reduction after 4–8 weeks (mean difference $= -1.69$ mmHg $[-2.22, -1.16]$, $P < 0.001$). In the RKI versus another medication class, IOP reduction by RKI was noninferior to timolol 0.5% twice-daily after 4–8 weeks (mean difference $= 0.39$ mmHg [0.01, 0.76], $P = 0.043$) and 12 weeks (mean difference $= 0.48$ mmHg [0.11, 0.85]; $P = 0.011$). In the subgroup analysis, the mean difference in IOP reduction by adjunctive RKI and placebo was -1.42 mmHg ($P < 0.001$). The most common ocular AE of RKI was conjunctival hyperemia (19–65%), followed by conjunctival hemorrhage (6–20%) and cornea verticillata (13–26%).

Conclusions With a treatment duration of 1–3 months, RKI showed effective IOP reduction noninferior to timolol as monotherapy and as adjunctive therapy. Our results suggested RKI be a reliable IOP control medication; however, its higher incidence of some ocular complications should be attended to.

Keywords Rho-kinase inhibitor · Ripasudil · Netarsudil · Intraocular pressure · Glaucoma · Efficacy · Ocular safety · Ocular adverse events

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Key messages

- Rho-kinase inhibitor (RKI) is a new medication for glaucoma; however, we are not aware of any published meta-analysis that systematically reviewed the IOP-lowering efficacy of RKI.

- With a treatment duration of 1-3 months, RKI showed effective IOP reduction as both monotherapy and adjunctive therapy.

- The short-term IOP-reducing effect of RKI is noninferior to timolol 0.5% twice-daily.

- The most frequent ocular adverse events observed with RKI treatment are conjunctival hyperemia,conjunctival hemorrhage, and cornea verticillate.

Introduction

Glaucoma is a leading cause of irreversible blindness worldwide [1]. Reduction of intraocular pressure (IOP) is the only proven treatment, and ocular hypotensive drugs are the first-line therapy for patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) [2, 3]. Although many anti-glaucoma agents are effective in lowering IOP, satisfactory control is sometimes not achieved even with maximum medical therapy. Therefore, novel medications have been explored as our understanding of glaucoma increased [4, 5].

Rho-kinase inhibitor (RKI) is a new medication in the ophthalmology field [6]. RKI was found to reduce IOP through alteration of the trabecular meshwork, thus enhancing aqueous humor outflow [7, 8]. Currently, there are two clinically approved RKI, ripasudil (K-115, Glanatec), and netarsudil (AR-11324, Rhopressa) [9]. Ripasudil was first approved in Japan in 2014 after clinical trials showed a significant dose-dependent IOP-lowering effect compared with placebo [10, 11]. In the phase 2 trial, twice-daily (BID) use of ripasudil 0.4% decreased IOP for > 3 mmHg after 8 weeks ($P < 0.05$) [11]. Netarsudil is an RKI and a norepinephrine transporter inhibitor [12]. Its clinical use was approved in the USA in 2017 after a randomized trial showed netarsudil 0.02% dosed daily (QD) produced significant IOP reduction after 4 weeks (5.7 mmHg, $P < 0.05$), which was only approximately 1 mmHg less effective than latanoprost 0.005% [13].

More large-scaled studies further examined the safety and efficacy of RKI since the clinical approval, including ROCKET 1–4, in which netarsudil 0.02% showed noninferiority to timolol 0.5% [14, 15], and the MERCURY 1–2, in which netarsudil 0.02%/latanoprost 0.005% combination showed superiority to its individual active components for one year [16, 17]. Although reported with a higher incidence of some ocular adverse events (AE), mainly conjunctival and corneal irritation, RKI is now considered a second-line treatment option for glaucoma and can be applied as both monotherapy and adjunctive therapy [9].

Despite more prevalent use in treating glaucoma, we are not aware of any published meta-analysis that systematically reviewed the IOP-lowering effect of RKI across different trial series. In the current study, we sought to provide better evidence for clinical use of RKI by examining its efficacy in different regimen types when compared with placebo or other anti-glaucoma agents and additionally reviewing its major ocular complications.

Methods

Literature search

This study was performed in accordance with PRISMA guidelines [18]. A literature search for studies published through March 20, 2021, was performed using PubMed and EMBASE and within the references of identified studies. Filters for "full text" in PubMed and "article" and "human" in EMBASE were applied. Major search key combination terms were "glaucoma OR intraocular pressure OR open angle glaucoma OR ocular hypertension OR normal tension glaucoma OR glaucoma suspect OR early glaucoma OR primary open angle glaucoma OR angle closure glaucoma OR POAG OR IOP" crossed with "rho kinase inhibitor OR ROCK inhibitor OR ripasudil OR Y-27632 OR netarsudil OR K-115 OR AR-13324 OR glanatec." Detailed search terms are provided in Online Resource 1.

Study selection

Study selection and data extraction were performed by two authors independently. After removing duplicates, title and abstracts were screened for eligibility. As efficacy is the main focus of the current study, study selection was based on the primary outcome-associated information. Studies evaluating the IOP-lowering efficacy of RKI in glaucoma were included. Non-human experiments, case

reports, conference, reviews, and meta- or pooled analysis were excluded. When multiple studies were derived from the same cohort with overlapping follow-up, only the latest was included. Retrieved studies then underwent full-text screening. We included only prospective, randomized control studies evaluating the efficacy of clinically approved RKI, netarsudil 0.02% QD and ripasudil 0.4% BID, against non-RKI regimen (placebo or other medications). A treatment duration longer than 4 weeks was required. Studies recruiting subjects with secondary glaucoma, angle-closure glaucoma, or recent glaucoma surgery were excluded. Studies with non-relevant results, ineligible study type, overlapping cohorts, or insufficient data were also excluded. Data insufficiency was defined as failure to provide explicit information about data relevant to subsequent analysis, which included sample size, study duration, and details of IOP measurements and medication regimen. The studies were further categorized into two classes. One class was RKI versus placebo, which included studies comparing RKI to placebo and studies comparing additive RKI on baseline treatment to the baseline treatment. The other class was RKI versus another medication, which included studies comparing RKI to another agent and studies comparing additive RKI to another additive agent on pre-existing treatment.

Data extraction

Data extraction was performed after the full-text screening. General information extracted included: first author, publication year, country, subject, treatment durations, evaluation intervals, and time of IOP measurement. Other efficacy-related variables extracted if available included regimens (drug species, types, concentrations, frequencies), sample sizes, baseline IOP, post-treatment IOP, IOP reduction, and difference in IOP reduction between the RKI and non-RKI group. Eligible studies were required to at least provide sample sizes and sufficient variables to generate the inter-group difference in IOP reduction. All treatment arms in one study were considered independent in the analysis, while only one set of data of the selected evaluation intervals in each treatment arm was used. For studies reporting IOP values at different time points, the mean diurnal IOP was calculated and used as a single measurement. The RevMan Calculator (Cochrane Training, 2020) was used to calculate the value of unprovided variables that can be directly derived from other data provided in the initial studies. For the evaluation of ocular safety, the reported incidences of the top three ocular AE in both RKI and non-RKI regimen groups, as defined by "Eye disorders" in the System Organ Classes and Preferred Terms of MedDRA, were extracted from all included studies if provided. Non-ocular AE and unspecified AE not definable by MedDRA were not extracted.

Data synthesis

Meta-analysis of the IOP-lowering effect of RKI was performed with a bivariate random-effects model. Inter-group differences in IOP reduction were pooled, with a mean difference < 0 favoring the use of RKI. Heterogeneity was evaluated using the Cochran Q statistic, which evaluated the variances across studies, and quantified with the I^2 statistic, which describes the variation of effect size that is attributable to between-study heterogeneity. The presence and effect of publication bias were examined using Deek's test. The funnel plots would appear asymmetrical if publication bias presents. Subgroup analysis for the IOP-lowering efficacy of RKI as adjunctive therapy versus placebo was also performed using the same method. All analyses were conducted with the Comprehensive Meta-analysis Software Version 3 (Biostat Inc., Englewood, NJ, USA). A two-sided P-value of 0.05 indicates statistical significance.

Results

Literature search

The literature search yielded 325 records from PubMed and 201 from EMBASE. One study was manually identified from the references. One hundred thirty-six duplicates were excluded. After title and abstract screening, we excluded 334 studies for non-relevant results, 15 for ineligible publication types, and one for overlapping cohorts. Forty-one studies went through the full-text screening, of which 20 were excluded for the non-relevant result, one for insufficient data, 2 for overlapping cohort, and 7 for ineligible study type. After study categorization, it was noted that only one study in the RKI versus another drug class used latanoprost while all others used timolol as a control regimen. To increase the validity of the analysis, the study was further excluded. To summarize, only 10 (2.6%) out of 391 studies were included for data analysis [11, 14, 15, 17, 19–24]. The flowchart of study selection was summarized in Online Resource 2.

Study characteristics

Non-RKI group major ocular AE [c] (%) Table 1 summarizes the relevant characteristics of included studies. All studies recruited subjects diagnosed with OAG or OHT, and the total number of initially enrolled subjects was 3412. The overall range of untreated IOP at the initial qualification visits was ≥ 15 and ≤ 36 mmHg across studies. All studies reported the occurrence of ocular AE in the testing population. Of the included studies, 3 (30%) evaluated the efficacy of Ripasudil 0.4% BID and 7 (70%) evaluated netarsudil 0.02% QD. For the RKI group regimen, 5 studies (50%)

Table 1 Summary of the relevant characteristics of the included studies

Study	Year	Country	Subjects	RKI Regimen(No. of subject[a])	Non-RKI Regimen (No. of subjects[a])	Study Duration	RKI Type	Time of IOP measurement	Evaluation intervals[b]	RKI group major ocular AE[c] (%)	Non-RKI group major ocular AE[c] (%)
Tanihara et al	2013	Japan	POAG or OHT (untreated IOP >= 21, <= 35mmHg)	ripasudil 0.4%, BID (49)	Placebo, BID (54)	8 wks	Single	9AM (trough), 11AM (peak), 5PM	8 wks	Conjunctival hyperemia (65%), Eye irritation (12%)	Conjunctival hyperemia (13%), Eye irritation (9%)
Tanihara et al	2015	Japan	POAG or OHT (untreated IOP >= 24, <= 35mmHg)	ripasudil 0.4% / timolol 0.5% FDC, BID (104)	Placebo / timolol 0.5%, BID (104)	8 wks	adjunctive	9AM (trough), 11AM (peak)	8 wks	Conjunctival hyperemia (65%), Eye irritation (11%), Allergic conjunctivitis/ Punctate keratosis (2%)	Conjunctival hyperemia (6%), Eye irritation (3%), Punctate keratosis (2%)
				ripasudil 0.4% /latanoprost 0.005% FDC, BID (102)	Placebo / latanoprost 0.005%, BID (103)					Conjunctival hyperemia (56%), Punctate keratosis/ Eye irritation (6%)	Conjunctival hyperemia (9%), Eye irritation (8%), Punctate keratosis (4%)
Inoue et al	2018	Japan	POAG[d]	ripasudil 0.4%, BID + PG analogs[e], QD (PM) (26)	timolol 0.5% /PG analogs FDC, QD (PM) (25)	3 mths	adjunctive	Mean diurnal value	1 mth, 3 mths	Conjunctival hyperemia (19%), Superficial punctate keratitis (15%), Lacrimation increased (4%)	Superficial punctate keratitis (20%), Eye irritation (16%), Vision blurred (8%)
Lewis et al	2016	United States	OAG or OHT (untreated IOP >= 24, <= 36mmHg)	netarsudil 0.02% / latanoprost 0.005% FDC, QD (PM) (73)	Placebo / latanoprost 0.005%, QD (PM) (73)	4 wks	adjunctive	Mean diurnal value	4 wks	Conjunctival hyperemia (40%), Conjunctival hemorrhage (7%), Lacrimation increased/ Eye pruritus (6%)	Conjunctival hyperemia (14%), Eye pruritus (3%), Lacrimation increased (1%)

Table 1 (continued)

Study	Year	Country	Subjects	RKI Regimen(No. of subjects[a])	Non-RKI Regimen (No. of subjects[a])	Study Duration	RKI Type	Time of IOP measurement	Evaluation intervals[b]	RKI group major ocular AE[c] (%)	Non-RKI group major ocular AE[c] (%)
Serle et al	2018	United States	OAG or OHT (untreated IOP > 20, < 27 mmHg)	netarsudil 0.02%, QD (PM) (202)	timolol 0.5%, BID (209)	3 mths	single	8AM, 10AM, 4PM	6 wks, 3 mths	Conjunctival hyperemia (53%), Conjunctival hemorrhage (13%), Eyelid erythema (6%)	Conjunctival hyperemia (8%), VA reduced (1%), Vision blurred/Eye irritation/ Conjunctival hemorrhage (1%)
Kahook et al	2019	United States	OAG or OHT (untreated IOP > 20, < 27 mmHg)[f]	netarsudil 0.02%, QD (PM) (251)	timolol 0.5%, BID (251)	12 mths	single	8AM, 10AM, 4PM	6 wks, 3 mths, 6 mths, 9 mths, 12 mths	Conjunctival hyperemia (61%), Cornea verticillata (26%), Conjunctival hemorrhage (20%)	Conjunctival hyperemia (14%), Eye irritation)/ Eye pain (3%)
Khouri et al	2019	United States	OAG or OHT (untreated IOP > 20, < 36mmHg)	netarsudil 0.02%, QD (PM) (351)	timolol 0.5%, BID (357)	3 mths	single	8AM, 10AM, 4PM	6 wks, 3 mths	Conjunctival hyperemia (48%), Cornea verticillata (25%), Conjunctival hemorrhage (16%)	Conjunctival hyperemia (9%), Conjunctival hemorrhage (3%), Lacrimation increased (1%)
Walters et al	2019	United States	OAG or OHT (untreated IOP > 20, < 30mmHg)	netarsudil 0.02% / latanoprost 0.005% FDC, QD (PM) (245)	Placebo / latanoprost 0.005%, QD (PM) (250)	3 mths	adjunctive	8AM, 10AM, 4PM, Mean diurnal value	6 wks, 3 mths	Conjunctival hyperemia (55%), Cornea verticillata (13%), Conjunctival hemorrhage (9%)	Conjunctival hyperemia (22%), Conjunctival hemorrhage (1%)

Table 1 (continued)

Study	Year	Country	Subjects	RKI Regimen(No. of subject[a])	Non-RKI Regimen (No. of subjects[a])	Study Duration	RKI Type	Time of IOP measurement	Evaluation intervals[b]	RKI group major ocular AE[c] (%)	Non-RKI group major ocular AE[c] (%)
Brubaker et al	2020	United States	OAG or OHT (untreated IOP >= 20, <= 36mmHg)	netarsudil 0.02% / latanoprost 0.005% FDC, QD (PM) (238)	Placebo / latanoprost 0.005%, QD (PM) (236)	12 mths	adjunctive	8AM, 10AM, 4PM, Mean diurnal value	6 wks, 3 mths, 6 mths, 9 mths, 12 mths	Conjunctival hyperemia (63%), Cornea verticillata (18%), Conjunctival hemorrhage (13%)	Conjunctival hyperemia (22%), Punctate keratosis (4%), VA reduced (3%)
Araie et al	2021	United States	POAG or OHT (untreated IOP >= 15, <= 35mmHg)	netarsudil 0.02%, QD (PM) (54)	Placebo, QD (PM) (55)	4 wks	single	Mean diurnal value	4 wks	Conjunctival hyperemia (37%), Eye irritation (9%), Conjunctival hemorrhage (6%)	Conjunctival hyperemia (2%)

[a]Number of enrolled subjects at the beginning of the study

[b]Only time intervals >= 4 weeks were presented

[c]Only the top 3 ocular AE with the highest incidences > 0% were presented

[d]No requirement for IOP was reported. The range of treated IOP of projects at inclusion was 11-24 mmHg

[e]Prostaglandin analogs used included latanoprost 0.005% and travoprost 0.004%

[f]The primary analysis population in this study were patient with baseline IOP < 25 mmHg

Abbreviation: *No.* = Number, *AE* = Adverse events, *IOP* = Intraocular pressure, *POAG* = Primary open angle glaucoma, *OHT* = Ocular hypertension, *OAG* = Open angle glaucoma, *FDC* = Fixed dose combination, *BID* = Twice daily, *QD* = Once daily, *PG* = Prostaglandin, *wks* = Weeks, *mths* = Months, *(PM)* = Administered at afternoon/night, *VA* = Visual acuity

Table 2 Pooled difference in intraocular pressure reduction between Rho-kinase inhibitor regimens and control regimens with the test for heterogeneity

Control group (treatment duration)	Number of data (studies)	Mean	SE	95% CI	P-value	Q-value	Df (Q)	P-value	I-squared
	Difference in IOP reduction (mmHg)				Test for heterogeneity				
Placebo (4–8 weeks)	7 (6)[a]	−1.69	0.27	(−2.22, −1.16)	<0.001	29.18	6	<0.001	79.44
Another drug[b] (4–8 weeks)	4 (4)	0.39	0.19	(0.01, 0.76)	0.043	4.23	3	0.237	29.12
Another drug[b] (12 weeks)	4 (4)	0.48	0.19	(0.11, 0.85)	0.011	3.16	3	0.368	4.97
Subgroup analysis	Number of data (studies)	Mean	SE	95% CI	P-value	Q-value	Df (Q)	P-value	I-squared
Adjunctive placebo (4–8 weeks)	5 (4)	−1.42	0.18	(−1.78, −1.06)	<0.001	8.22	4	0.084	51.34

[a]One study contained two treatment arms

[b]The control drug in the included studies was timolol 0.5%, dosed twice daily

Abbreviation: *IOP*, intraocular pressure; *SE*, standard error; *CI*, confidence interval; *Df (Q)*, degrees of freedom (*Q*)
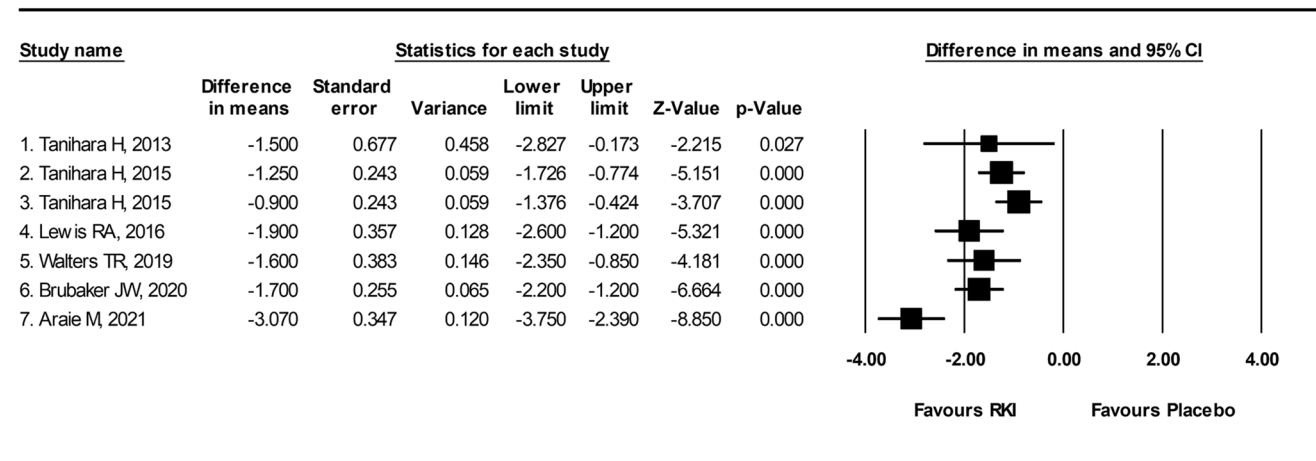

Fig. 1 Summary of data of Rho-kinase inhibitor versus placebo comparison (4–8 weeks)

evaluated its efficacy as monotherapy, and 5 (50%) evaluated its additive IOP-lowering effect. The follow-up duration ranged from 4 weeks to 12 months, with 6 (60%) lasting for longer than 3 months. For the time of IOP measurement, 7 studies (70%) initially provided IOP values at more than one time point in a day for at least one evaluation interval, while 3 (30%) provided only mean diurnal IOP. The funnel plot for all included studies was presented in Online Resource 3, with no visually significant asymmetry found.

Efficacy: RKI versus placebo

Six studies (60%) were classified as RKI versus placebo [11, 17, 19, 21, 23, 24], with one containing 2 treatment arms [19]. The study by Araie et al. and Tanihara et al. compared the efficacy of netarsudil and ripasudil as monotherapy against placebo for 2 and 1 month, respectively [11, 24]. Lewis et al., Walters et al., and Brubaker et al. compared the additive effect of netarsudil on latanoprost 0.005% QD for up to 1, 3, and 12 months, respectively [17, 21, 23].

Another study by Tanihara et al. in 2015 examined ripasudil as adjunctive medication against placebo for both timolol 0.5% and latanoprost 0.005% therapies for 2 months [19]. The funnel plot for this class was presented in Online Resource 4, and there was no significant bias.

After evaluation, data of a treatment duration of 4–8 weeks were pooled. The result of the pooled difference in IOP reduction and test for heterogeneity is summarized in Table 2. Summary of data was also presented (Fig. 1). The RKI regimen group showed significantly greater IOP reduction compared with the non-RKI regimen group, with a mean pooled difference of −1.69 mmHg (−2.22, −1.16; $P < 0.001$). The heterogeneity was significant ($I^2 = 79.44$, $P < 0.001$). For subgroup analysis of RKI as an adjunctive medication (Table 2), a similar result was found, with a slightly decreased but still significant mean pooled difference of −1.42 mmHg (−1.78, −1.06; $P < 0.001$). Summary of subgroup data was shown in Online Resource 5, and the heterogeneity was non-significant ($I^2 = 51.34$, $P = 0.084$).
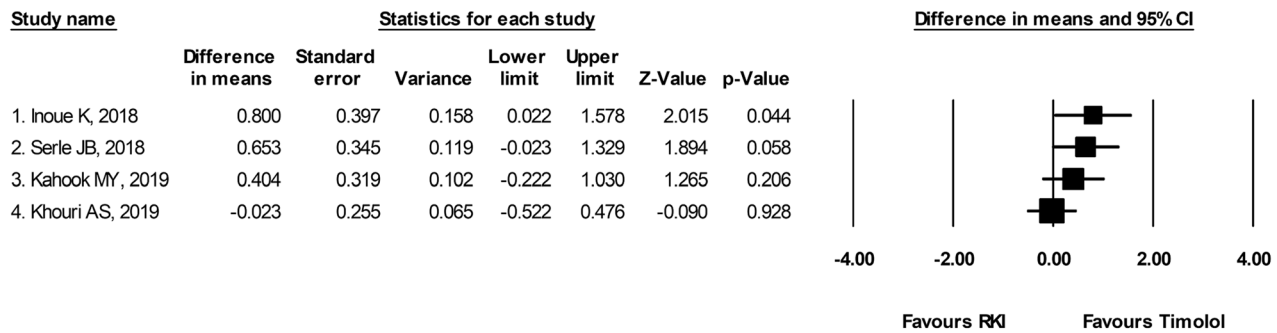
Study name	Statistics for each study							Difference in means and 95% CI
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
1. Inoue K, 2018	0.800	0.397	0.158	0.022	1.578	2.015	0.044	
2. Serle JB, 2018	0.653	0.345	0.119	-0.023	1.329	1.894	0.058	
3. Kahook MY, 2019	0.404	0.319	0.102	-0.222	1.030	1.265	0.206	
4. Khouri AS, 2019	-0.023	0.255	0.065	-0.522	0.476	-0.090	0.928	

-4.00   -2.00   0.00   2.00   4.00

Favours RKI   Favours Timolol

Fig. 2 Summary of data of Rho-kinase inhibitor versus timolol comparison (4–8 weeks)

Study name	Statistics for each study							Difference in means and 95% CI
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
1. Inoue K, 2018	0.300	0.523	0.273	-0.725	1.325	0.574	0.566	
2. Serle JB, 2018	1.009	0.352	0.124	0.318	1.700	2.863	0.004	
3. Kahook MY, 2019	0.352	0.369	0.136	-0.370	1.074	0.955	0.340	
4. Khouri AS, 2019	0.233	0.303	0.092	-0.360	0.826	0.770	0.442	

-4.00   -2.00   0.00   2.00   4.00
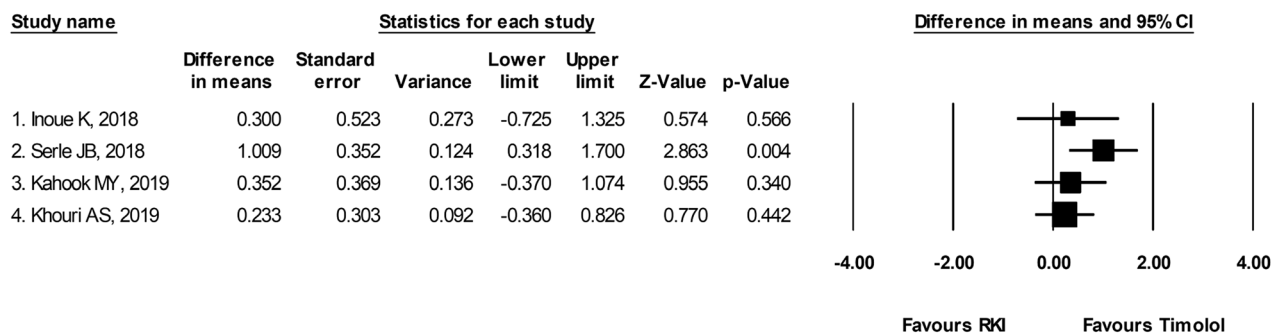
Favours RKI   Favours Timolol

Fig. 3 Summary of data of Rho-kinase inhibitor versus timolol comparison (12 weeks)

Efficacy: RKI versus timolol

Four studies (40%) evaluated the efficacy of RKI versus another drug [14, 15, 20, 22]. In this meta-analysis, the control medications were all timolol 0.5% BID. A study by Inoue et al. compared adding ripasudil to prostaglandin analogs to a switch from prostaglandin analogs to timolol/prostaglandin combination, BID for 3 months [20]. Serle et al., Kahook et al., and Khouri et al. evaluated the efficacy of netarsudil as monotherapy against timolol for up to 3, 12, and 3 months, respectively [14, 15, 22].

After evaluation, data with treatment durations of 4–8 weeks and 12 weeks were collected and pooled separately (Table 2). Summary of data was presented in Figs. 2 and Fig. 3. After 4–8 weeks, the RKI regimen group showed a slightly lesser IOP reduction compared with the non-RKI regimen group, with a mean pooled difference of 0.39 mmHg (0.01, 0.76; $P = 0.043$). The heterogeneity was non-significant ($I^2 = 29.12$, $P = 0.237$). Similar result was found for 12-week data, with a mean pooled difference of

0.480 mmHg (0.11, 0.85; $P = 0.011$) and non-significant heterogeneity ($I^2 = 4.97$, $P = 0.368$).

Safety: major ocular complications

Summary of the major ocular AE in the included studies was presented in Table 1. Overall, the most frequent ocular complication in the RKI regimen group was conjunctival hyperemia, followed by conjunctival hemorrhage and cornea verticillata. The incidence of conjunctival hyperemia in RKI groups ranged from 37–65% when administered as monotherapy and 19–65% as adjunctive therapy, with most studies showing > 40% affected [11, 14, 15, 17, 21–23, 25]. In comparison, the ranges of incidence of conjunctival hyperemia were 8–14% and 9–22% for timolol and latanoprost treatment [14, 15, 17, 19, 21–23], respectively ($P < 0.01$ for all). Incidence of conjunctival hemorrhage in the RKI groups ranged from 6–20% [14, 15, 17, 21–24] and that of cornea verticillate ranged from 13–26% [14, 17, 22, 23]. Although conjunctival hemorrhage was occasionally observed with a non-RKI regimen (1–3%) [15, 17, 22], no included study

reported cornea verticillata in non-RKI groups. It was also noted that only netarsudil studies reported cornea verticillata as a major ocular AE [14, 17, 22, 23]. Occurrence of most other agent-unspecific ocular AE, including eye irritation or pruritus (< 10–15%), lacrimation increase (< 5%), and blurred or reduced vision (< 10%), was mostly slightly increased in the RKI groups or comparable between the two groups.

Discussion

In the current study, the IOP-lowering efficacy of RKI compared with placebo or other agents with 1–3 months of treatment was the primary outcome. Compared with placebo, RKI showed greater efficacy as monotherapy and as adjunctive therapy, consistent with prior individual studies [19, 26, 27]. The greater heterogeneity in the RKI versus placebo class was unsurprising due to the varying control group regimens across studies. However, it is arguable that the effect of medication may differ when used alone or adjunctively [28–31]. Therefore, a subgroup analysis was performed to examine specifically the additive efficacy of RKI, and a significant result was shown. It should be noted that the heterogeneity was not significant in the subgroup analysis. Given that fewer data were included in the subgroup, a true decrease in heterogeneity was further confirmed with a decreased tau value (subgroup: 0.29; all: 0.62). The result agreed with the assumption of a greater between-study variance of the RKI versus placebo class resulted from the varying control group regimens.

A few studies have examined the effect of RKI as adjunctive therapy. The MERCURY studies were phase 3, superiority trials evaluating netarsudil/latanoprost combination, QD against its active components [17, 23]. The criteria for superiority was $P < 0.05$ and a difference in mean IOP reduction < 0 at all time points of all visits. MERCURY-1 showed the superiority of the combination drug to latanoprost, with a mean difference in IOP reduction of − 1.7 mmHg after 3 months. MERCURY-2 also proved the superiority of adjunctive netarsudil therapy, with a mean difference of − 1.4 mmHg compared with latanoprost after 3 and 12 months. Tanihara et al. examined the addition of ripasudil to latanoprost and timolol, and the differences in IOP reduction were − 0.4 to − 1.4 mmHg and − 0.9 to − 1.6 mmHg, respectively ($P < 0.05$ for both) [19]. Our subgroup analysis result supported that adjunctive RKI is effective in IOP reduction, with a pooled mean difference within the previously reported ranges.

When comparing RKI with another anti-glaucoma agent, we found a slightly lesser IOP reduction by RKI than timolol that fulfilled noninferiority [15]. To the best of our knowledge, the efficacy of RKI has not been examined across different trial series, and the only pooled analysis was conducted by the ROCKET research group using their own data [32]. The ROCKET studies were noninferiority trials comparing netarsudil 0.02% QD to timolol 0.5% BID [14, 15], with noninferiority defined as a 95% confidence interval upper limit around the difference within 1.5 mmHg at all time points and within 1.0 mm Hg at most time points. In ROCKET-1, noninferiority was not met in primary analysis after 3 months but was met for post hoc analysis on patients with baseline IOP < 25 mmHg. In ROCKET-2, these subjects became the primary analysis population, and noninferiority was met again [15]. In ROCKET-4, a larger population was included [22], and noninferiority was finally proven in patients with baseline IOP < 27 mmHg and < 30 mmHg after 3 months. Interestingly, in the ROCKET pooled analysis, patients with baseline IOP < 25 mmHg were still chosen as the primary population. Similar to our result, they concluded that netarsudil was noninferior to timolol, although a wider range of inclusion IOP was validated in our study [32].

For a precise estimation, only data derived from selected evaluation intervals were pooled in this meta-analysis. Different from most established anti-glaucoma agents, RKI is known to improve IOP through modifying the trabecular meshwork [9, 33, 34]. As a result, it was presumed to be used adjunctively rather than applied alone, and most trials have been short-term studies evaluating its additive efficacy [9]. Due to relatively few long-term prospective trials for RKI, the optimal treatment duration needed to reach effect stability remains elusive. In ROCKET-2, IOP measurement at 8 AM continued for 12 months, yet the result fluctuated throughout the study period [14]. In MERCURY-1, the greatest mean difference between netarsudil/latanoprost combination and latanoprost happened around 6 weeks, and no obvious additional decrease was noted after 3 months during the 1-year follow-up [23]. In the retrospective study by Tanihara et al., the efficacy of monotherapy and adjunctive ripasudil was sustained for 52 weeks, but the IOP level at 52 weeks did not differ significantly from that at 28 weeks [25]. Other long-term, retrospective studies for ripasudil also showed post-treatment IOP that stabilized after 1 and 3 months [35, 36]. Although a comparison between different treatment intervals was not performed, the plateau of IOP reduction by RKI was likely met between 6 weeks to 3 months based on prior results, consistent with the selected evaluation interval in this study.

Briefly, the efficacy of RKI seems to be noninferior to established first-line anti-glaucoma agents with a short-term use, and its greatest utility is likely when applied as adjunctive or second-line medication. In the study by Inazaki et al., the long-term additive effect of ripasudil on maximal medication therapy was tested, and significant IOP reduction of − 2.8 and − 2.6 mmHg was shown after 3 and 12 months [37, 38]. Woolf et al. also found a significant IOP reduction

by netarsudil in patients with maximal medication compared with latanoprostene bunod 0.024% or a fourth medication [39]. These results indicated that adjunctive use of RKI may be beneficial for advanced cases with inadequate IOP control. Nevertheless, one major drawback of RKI is its higher incidence of some ocular AE compared to other anti-glaucoma medications, as reported in past studies [11, 21, 24, 35, 40, 41]. This should be especially attended to when prescribing to patients with poor IOP control, as they are more prone to ocular surface disease due to pre-existing heavier drug burden [42, 43].

In the current study, we additionally reviewed the major ocular AE of RKI, particularly those RKI-specific ones, as the ocular tolerance of anti-glaucoma agents has a great impact on patient compliance and may directly affect the treatment success [42, 44–46]. Conjunctival hyperemia was the most frequent AE observed with RKI, which is likely related to conjunctival vessel relaxation [47]. Although it is also widely observed in other IOP-reducing agents, especially prostaglandin analogs [48, 49], the reported occurrences with RKI were still significantly higher with most incidence > 40% [6, 11, 14, 15, 17, 19, 21–23, 32]. Fortunately, this AE was predominantly asymptomatic or mild in presentation. Other top ocular AE found were conjunctival hemorrhage and cornea verticillata, usually reported in 10–20% of patients and were more often seen with netarsudil. Despite the lower incidence compared with conjunctival hyperemia, conjunctival hemorrhage and cornea verticillata are more specific to RKI, as their occurrences were usually < 3% with other anti-glaucoma treatment [15, 17, 22]. Similarly, they are usually mild or moderate in presentation, with no apparent effect on vision and spontaneous resolution after medication discontinuation. While most major ocular AE associated with RKI seemed manageable, more long-term studies are needed to conclude its ocular safety. For ophthalmologists, it is essential to keep in mind that although IOP control is important in managing glaucoma, the ocular tolerability of the medication should be weighed when making prescription decisions.

Limitations

Several observations should be noted when interpreting this study. First, although the analysis was conducted based on study design and treatment duration, possible residual heterogeneity across studies should still be considered, including the disease severity, drug species, and the interval between eyedrop administration and IOP measurements. Second, we could not fully evaluate the effect of RKI at different time points. However, a reliable estimation of its efficacy on lowering mean diurnal IOP was provided, which is still of clinical importance. Third, since RKI is not yet available in some countries, the included studies

were conducted mainly in Japan and the USA, where the patient profiles and disease presentation could be different. Therefore, the generalizability of these results needs further confirmation. Lastly, glaucoma patients are usually prescribed multi-drug therapy, especially poorly controlled cases [37, 50], and our study may not fully reflect the efficacy of RKI in a real-world scenario for a particular population.

In conclusion, the current meta-analysis examined the IOP-lowering efficacy of RKI with a treatment duration of 1–3 months and reviewed its ocular safety. Overall, RKI is effective and noninferior to timolol in reducing IOP as monotherapy and as adjunctive therapy, and our result suggested it is a reliable option for IOP control in glaucoma patients. However, RKI possesses a higher incidence of some ocular complications, most notably conjunctival hyperemia, which should be considered when making the prescription decision. Future long-term studies comparing the safety and efficacy of RKI with various other anti-glaucoma agents are needed for a more comprehensive evaluation of the clinical usefulness of this medication.

Author contribution Study concept and design: Wu J.H., Chang S.N., Lin J.W.

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Analysis and interpretation of data: Wu J.H., Chang S.N., Takashi N., Kuo B.I., Lin J.W.

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Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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