

Netarsudil: a novel intra-ocular pressure lowering agent**Ravi R. Ghanghas, Prafull Mohan*, Vikrant Sharma, Ashok K. Sharma**

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ABSTRACT

Optic disc health is an important indicator of visual functions. The first line of management to prevent/halt the damage to optic disc is to control responsible pathological condition, if identified. In absence of identifiable cause, the most validated approach is lowering of intra-ocular pressure (IOP). Individually, as well as combinations of currently available drugs are not fully effective in all patients of glaucoma in achieving desired IOP control. Hence, there is a need of newer alternatives which address this unmet need. Recently, a newer IOP lowering agent with a novel mechanism of action, netarsudil, has been approved by United States Food and Drug Administration (US-FDA) in December 2017. Netarsudil acts by inhibiting Rho-associated protein kinase resulting in lowering of overall tone of the contractile cells in trabecular meshwork thereby improving drainage of aqueous humor outflow and lowering of IOP. Though in its early days, this drug gives an armamentarium to ophthalmologists and physicians to control IOP in patients of open-angle glaucoma and ocular hypertension.

Keywords: Intra-ocular pressure, Netarsudil, Rho kinase inhibitor**INTRODUCTION**

Optic disc health is an important indicator of visual functions. Damage to the optic disc results from raised intra-ocular pressure (IOP), vascular insufficiency, altered immunity, oxidative stress, etc. developing due to pathological conditions like compressive lesions of the brain that raise intra-cranial pressure, systemic diseases like diabetes mellitus, hypertension, genetic factors, cigarette smoking and corticosteroid therapy, etc.¹ The first line of management to prevent/halt the damage to optic disc is to control responsible pathological condition, if identified. In absence of identifiable cause, the most validated approach is lowering of IOP.² The benefits of lowering IOP on optic disc health have been observed not

only in glaucoma patients with raised IOP (>21mm Hg) but also in patients with optic disc changes with IOP in normal range (i.e. patients with normal-tension glaucoma).³

Lowering of IOP reduces mechanical strain of aqueous humor on posterior structures of the eye, thereby arresting glaucomatous changes in optic disc and can be achieved by reducing aqueous humor production or improving drainage. Rate of aqueous humor production can be reduced by drugs which include β -adrenergic blockers, α -adrenergic agonists and carbonic anhydrase inhibitors whereas drainage of aqueous humor may be improved by miotics like cholinergic drugs (mainly trabecular outflow),

α -adrenergic agonists and prostaglandin (PG) analogues (largely uveoscleral outflow).

Individually, as well as combinations of these drugs are not fully effective in all cases of glaucoma in achieving desired IOP control.⁴ In addition, these drugs also have certain limitations. β -adrenergic blockers are traditionally contraindicated in patients with cardiac diseases (severe bradycardia, heart block) and bronchial asthma. α -adrenergic agonists are contraindicated in patients with narrow irido-corneal angle. PG analogues are known to cause cosmetic ocular adverse effects (eyelid skin darkening, increased iris pigmentation) which may be undesirable, especially in younger patients. Cholinergic drugs are poorly tolerated and produce accommodation disturbances, brow-ache, and diminution of vision in dim light. Hence, there is a need of newer alternatives which address this unmet need. Recently, a newer IOP lowering agent with a novel mechanism of action, netarsudil, has been approved by United States Food and Drug Administration (US-FDA) in December 2017.⁵

CHEMISTRY OF NETARSUDIL

Netarsudil is chemically (S)-4-(3-amino-1-(isoquinolin-6-yl-amino)-1-oxopropan-2-yl) benzyl 2,4-dimethylbenzoate. The molecular weight of the free base is 453.54 and that of its dimesylate salt, which is used clinically, is 645.74.

MECHANISM OF ACTION

Netarsudil is an inhibitor of Rho-associated Protein kinase (ROCK), a serine/threonine kinase.⁶ ROCK is responsible for cytoskeleton changes in trabecular meshwork like actin-membrane linkage, cell contraction, promotes extracellular matrix production etc. leading to increased resistance of trabecular pathway which subsequently reduces aqueous humor drainage and ultimately increases IOP. Netarsudil on the other hand, reduces fibrotic material deposition in trabecular meshwork and relaxes the overall tone of the contractile cells in trabecular meshwork thereby improving drainage of aqueous humor outflow resulting in lowering of IOP.⁷ Apart from this, Netarsudil has inhibitory activity against the norepinephrine transporter (NET), by virtue of which this drug is believed to reduce aqueous humor production and also improve its drainage (trabecular pathway) adding to IOP lowering action.⁸ However, this action has not been fully elucidated.

PHARMACOKINETICS

On topical administration, Netarsudil has good penetration through cornea. It is mainly metabolized by esterases in the eye to its five-time potent active metabolite, netarsudil-M1. Netarsudil and its metabolite reach their peak action at around eight hours of dosing and IOP lowering action lasts for at least 24 hours.⁹ Both Netarsudil and its active metabolite have shown minimal systemic absorption and are highly plasma-protein bound (>60%). Half-life of

Netarsudil is nearly 3 hours (approximately 175 minutes) whereas that of its metabolite M1 has not been fully evaluated.

CLINICAL TRIAL DATA OF NETARSUDIL

The FDA approval of netarsudil is based on clinical efficacy of two phase 3 randomised trials. Netarsudil was compared with timolol, which is considered standard of therapy for glaucoma worldwide.¹⁰

The first trial, Rho Kinase Elevated IOP Treatment Trial 1 (ROCKET-1) trial was a double-masked, randomized, non-inferiority clinical trial conducted with netarsudil 0.02% administered once-daily versus timolol 0.05% ophthalmic solution administered twice daily. ROCKET-1 included 411 adults (aged 18 years or above) with IOP <27 mm Hg of Whites or African-American patients of Primary-open angle-glaucoma or ocular hypertension. After wash-out period, both groups received respective therapies and analysed for three-month duration. The mean IOP in netarsudil group ranging from 21.8 - 23.4mm Hg at baseline reduced to 17.2 - 19.8mm Hg, while in Timolol group mean IOP ranging from 21.5 - 23.4mm Hg decreased to 17.4 - 18.5mm Hg across the nine treatment time points. Netarsudil did not meet its primary efficacy endpoint at three of the nine endpoints. However, in a post-hoc analysis with patients having baseline IOP less than 25mm Hg, it demonstrated non-inferiority of IOP lowering compared to timolol.

The other phase 3 clinical trial (ROCKET-2) was also double-masked, randomized non-inferiority clinical trial conducted with netarsudil dosed twice-daily versus timolol administered twice daily. This trial was conducted in a sequential manner and first phase was similar to ROCKET-1. If netarsudil in once-daily dosing demonstrated non-inferiority versus timolol the dose of netarsudil was increased to twice-daily regimen. The primary analysis population for efficacy was the per protocol population with an IOP lesser than ROCKET-1, i.e. subjects with pre-study baseline IOPs of 20 to 25 mm Hg. This trial had larger sample size (n=756) and the other demographics were similar to ROCKET-1, except a lower frequency of brown/black iris colour. Both groups of netarsudil (once-daily and twice-daily regimen) in ROCKET-2 achieved the primary efficacy endpoint of reduction of IOP. This trial has been extended to 12 months period and another trial (ROCKET-4) with higher baseline IOP (up to 30mm Hg) has been recently completed and results will throw more data on this drug.¹¹

SIDE-EFFECTS OF NETARSUDIL

Once-daily dosing of netarsudil has been found to be generally well-tolerated as compared to twice-daily dosing.¹⁰ The most common ocular adverse reaction observed with netarsudil has been conjunctival hyperaemia which has been reported in nearly half of the patients, even with once-daily dosing. Other less common

adverse reactions are: corneal verticillata (whorl-like pattern of corneal deposits), instillation site pain, and conjunctival haemorrhage but are well-tolerated. Adverse effects least common are instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity.

CONTRA-INDICATIONS AND PRECAUTIONS

There are no contraindications to netarsudil as per FDA label but patients with known hypersensitivity to its preservative (benzalkonium chloride) should not be prescribed this drug.⁵ In addition, use of contact lenses warrants their removal prior to instillation of netarsudil and they may be reinserted 15 minutes following the eye drops instillation. The universal precautions applicable to use of eye drops also apply to netarsudil, including a gap of five minutes between instillation of other eye drops.

There is no clinical data of use of netarsudil in pregnant and lactating women. Safety and effectiveness of netarsudil in paediatric patients below the age of 18 years has not been established.

DOSING AND INDICATIONS

Netarsudil is available as 0.02% eye drops (which contains 0.2 mg per mL of netarsudil) and is to be used once-daily (instilled as single drop in each eye), preferably in the evening. The approved indications are reduction of IOP in patients with optic disc changes (glaucoma) or without optic disc changes (ocular hypertension).⁵

CONCLUSION

Netarsudil has a novel mechanism of action and promises to have synergistic action with other established drugs in lowering of IOP. Though in its early days, this drug gives an armamentarium to ophthalmologists and physicians to control IOP in patients of open-angle glaucoma and ocular hypertension.

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