Rho kinase inhibitor for primary open-angle glaucoma and ocular hypertension

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A systematic review to assess the evidence on the efficacy and safety of rho kinase inhibitors for topical treatment of glaucoma and ocular hypertension

Rationale

Conventional topical treatments for glaucoma include prostaglandin analogues (PAs) and beta-blockers (BBs) to lower intraocular pressure (IOP)

Rho kinase inhibitors (ROKis) target trabecular meshwork and Schlemm's canal to increase drainage of aqueous humour and thus reduce IOP

ROKis are approved to treat glaucoma in Japan (2014), USA (2017) and Europe (2019)

Aim: To compare the efficacy and safety of commercially available topical formulations of ROKis with placebo and other topical antiglaucoma medications in people diagnosed with open-angle glaucoma (OAG), primary open-angle glaucoma (POAG) or ocular hypertension (OHT).

Search strategy

Databases searched on 11 December 2020 → 555 records (551 studies) after removal of duplicates → 17 trials for analysis from Japan, USA and Canada; 15 included in meta-analyses (13 – IOP outcomes reported, 15 – AE outcomes reported) → Total 4,953 adult participants, all diagnosed with (P)OAG or OHT

Systematic review of randomised controlled trials

Conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*

Certainty of evidence analysed by two reviewers using the GRADE approach[1]: *high, moderate, low or very low*

Primary outcome: Glaucoma progression – additional visual field defects from baseline at ≥12 months follow-up

Secondary outcome: Six measures, including:
Mean difference in IOP – baseline vs follow-up

Severity and number of adverse events (AEs)

Interventions in included trials

Trials compared ROKi monotherapy (netarsudil or ripasudil) or combination therapy with placebo, PA (latanoprost) or BB (timolol)

- Netarsudil-based (15)
  - N monotherapy (12)
    - N vs placebo (4)
    - N vs T (4)
    - N vs L (4)
  - N combination therapy (3)
    - N vs N/L (3)
- Ripasudil-based (5)
  - R monotherapy (2)
    - R vs placebo (2)
  - R combination therapy (3)
    - R+T/R+L vs L/T (2)
    - R+L/other vs T+L/O (1)

Number of trials in brackets; L, latanoprost; N, netarsudil; O, other prostaglandin analogue; R, ripasudil; T, timolol

Quality of evidence

Small number of trials

No trials reported primary outcome of glaucoma progression at ≥12 months

Only 2 of the 6 secondary outcomes reported in any trials: changes in IOP and ocular AEs

Most trials evaluated short-term effects only (24 h to 6 months)

Certainty of evidence very low or low for all comparisons except timolol

Risk of bias high in 3 trials (IOP) and 8 trials (AEs)

Takeaways
(with reservations about quality of evidence)

Efficacy

ROKi monotherapy may reduce IOP in people with OAG or OHT

Netarsudil monotherapy may be inferior to latanoprost monotherapy and slightly inferior to timolol

Netarsudil + latanoprost/timolol probably reduces IOP more than monotherapy

Recommendation

Trials with longer follow-up and primary outcome of disease progression, not only IOP reduction

Safety

Most frequently reported ocular AEs:

conjunctival hyperaemia

ocular pain/irritation

No serious AEs with ROKi therapy

ROKi monotherapy/combination therapy may cause more ocular AEs, compared with latanoprost and timolol monotherapy – evidence certainty low or very low for all comparisons except timolol (moderate certainty)

Recommendation

Trials use standardised terminology and detailed description of AEs

Reference

1. Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html

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