A Balancing Act: Low-dose Atropine Significantly Slows Pediatric Myopia Progression Without A Clinically Meaningful Risk of Rebound

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J. JOVANOVIĆ[1], M. ZACHARIOUDAKI[2], G. PAPADAKIS[3], M. KALATZI[3], N. MULKALAPALLI[4], F. ERNST[5], T. DE MILLIANO[6]

[1]IQVIA, London, United Kingdom, [2]IQVIA, Munich, Germany, [3]IQVIA, Athens, Greece, [4]IQVIA, Gurugram, India, [5]Santen Pharmaceuticals, Munich, Germany, [6]Santen, Geneva, Switzerland

INTRODUCTION

- **Myopia** is an **ophthalmic disease** that manifests as refractive error caused by excessive axial elongation of the eye [(1)]. In myopic eyes, light rays parallel to their optical axis focus in front of the retina when accommodation is relaxed, resulting in **blurred distance vision**[(2)]. Progression of myopia can be rapid in children and adolescents due to eye growth in that period, and is associated with ocular complications that may cause irreversible visual impairment in later life[(3)]. Adolescent myopia **prevalence is projected to reach 47% globally by 2050**[(4)].
- In regions offering multiple interventions to slow myopia progression that have not been compared head-to-head in an RCT, **indirect treatment comparisons are necessary to support HTA**, which relies on treatment ranking by efficacy/safety with associated uncertainty.

OBJECTIVE

To evaluate **the comparative efficacy and safety of low-dose atropine (LDA)** versus other pharmacological, optical or light-based therapies for slowing pediatric myopia progression in a network meta-analysis.

METHODS

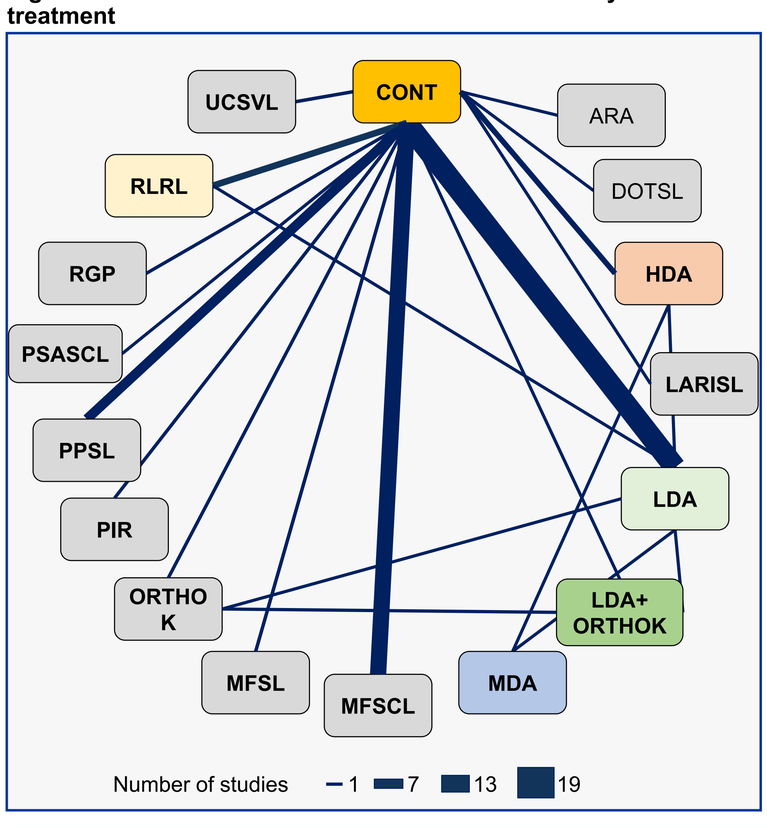
- **A systematic literature review (SLR)** was performed to identify, evaluate, and qualitatively synthesize clinical evidence on current treatment options for pediatric myopia.
- **The atropine treatments included in the network of evidence** were grouped by dosage: low-dose (<0.1% atropine, LDA), moderate-dose (≥0.1% & <0.5% atropine, MDA) and high-dose (≥0.5%, HDA).
- **Outcomes of interest** included change from baseline (CFB) in spherical equivalent refraction (SER) or axial length (AL) through 1, 2 and 3 years of treatment, annual progression rate (APR) through 2 years of treatment and rebound effect (change in SER or AL 1 year after treatment cessation).
- **A Bayesian NMA** was performed using Hamiltonian Monte Carlo. Because outcomes were continuous, we used a normal likelihood with an identity link. Both fixed-effects (FE) and random effects (RE) models were fit to the data. Model selection was based on the deviance information criterion (DIC). Inconsistency assessment was applied to networks with closed loops[(5)].
- **Heterogeneity,** defined as the variation in the true effect size between RCTs included in the analyses stemming from clinical or methodological differences or simply chance, was evaluated qualitatively and examined quantitatively through subgroup analyses and network meta-regressions[(6)].

RESULTS

Systematic review and ITC feasibility assessment

- The SLR identified 117 RCTs of 24 active interventions. Twenty-two RCTs were excluded due to heterogeneity or high risk of bias**.**
- 69 RCTs of 16 active interventions were included in the network of evidence for the CFB in SER at year 1 (Figure 1), while the evidence base for the analyses of CFB in AL at year 1 comprised 80 studies of 17 active interventions.
- The network of evidence for the analyses of rebound effect on SER or AL included 6 RCTs comparing 3 active interventions

Figure 1. Network of evidence for CFB in SER after 1 year of treatment



Efficacy of LDA versus other myopia control options

- The RE model provided better fit to the data across all analyses and it was therefore used for inference.
- **LDA** was superior to inactive control or UCSVL in slowing pediatric myopia progression measured by CFB in SER or AL over a treatment period of at least two years (Figure 2 and Figure 3).

Figure 2. Change from baseline in SER after 1 year of treatment (D)

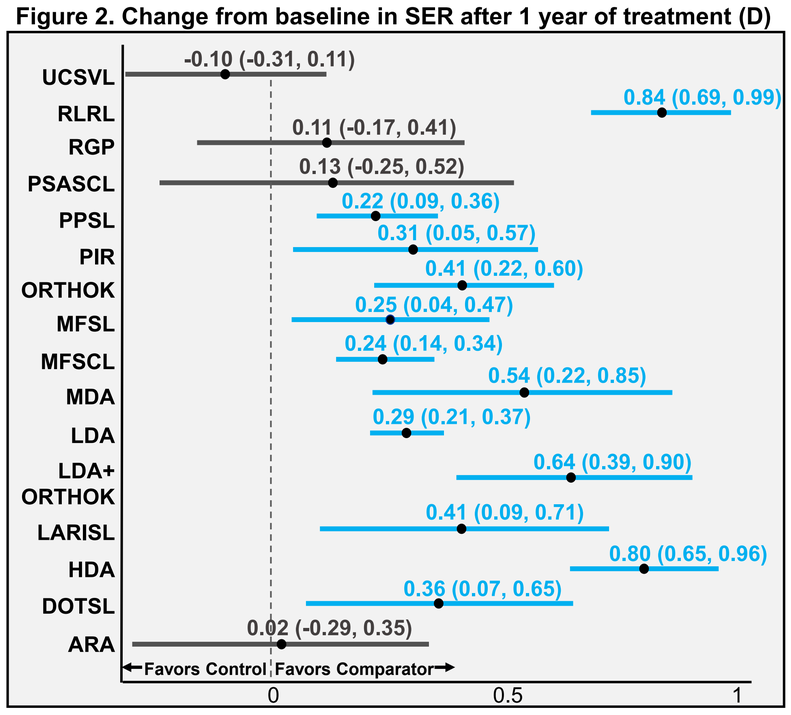
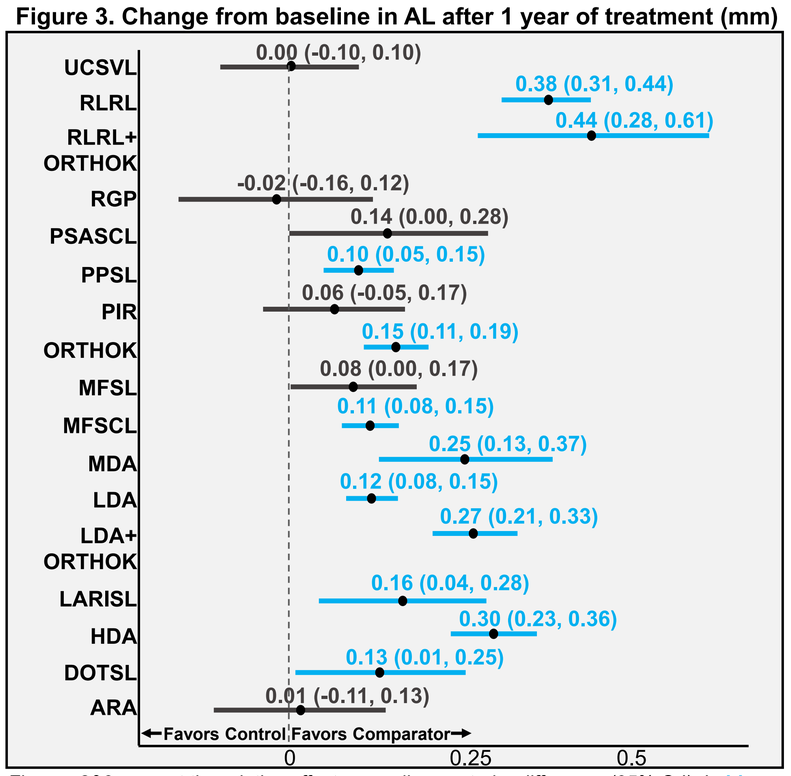


Figure 3. Change from baseline in AL after 1 year of treatment (mm)



Figures 2&3 present the relative effect as median posterior difference (95% CrI). In **blue**, statistically significant; In **grey**, not statistically significant. Reference treatment is control.

- LDA was numerically but not significantly superior to ARA, MFSCL, MFSL, PPSL, PSASCL and RGP, likely due to insufficient evidence and heterogeneity. After 1 year, HDA, LDA + ORTHOK, RLRL alone or in combination with ORTHOK were significantly superior to LDA in either CFB in SER or CFB in AL. At year 2, only HDA and LDA+ORTHO-K were significantly more effective than LDA (only year 1 CFB in AL was reported for RLRL + ORTHOK) (Table 1).

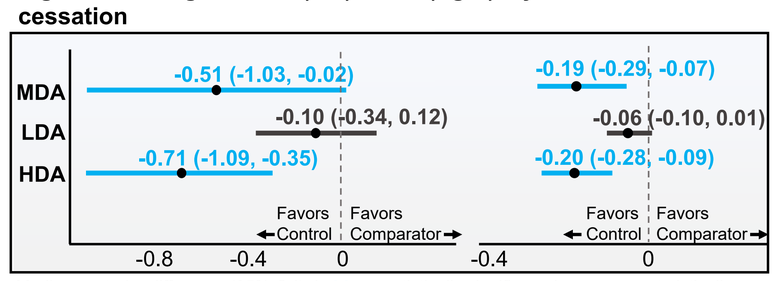
Table 1. Posterior rank mean (SD) for CFB in SER or AL

Treatment (in alphabetical order)	Posterior rank [Mean (SD)]			
	SER		AL	
	Year 1	Year 2	Year 1	Year 2
ARA	**14.45** (2.47)	NA	**15.34** (2.41)	NA
CONT	**15.24** (0.87)	**10** (0.72)	**16.21** (0.96)	**11.53** (0.84)
DOTSL	**7.71** (3.03)	**4.64** (2.56)	**9.63** (3.2)	**6.11** (2.65)
HDA	**1.84** (0.72)	**1.37** (0.62)	**3.46** (0.82)	**2.35** (1.07)
LARISL	**6.86** (2.94)	NA	**8.01** (2.89)	NA
LDA	**8.99** (1.54)	**5.38** (1.48)	**10.18** (1.57)	**7.29** (1.34)
LDA + ORTHOK	**3.35** (1.2)	NA	**4.28** (0.9)	**1.75** (1.01)
MDA	**4.69** (2.15)	**3.09** (2.03)	**4.78** (1.66)	**3.25** (1.94)
MFSCL	**10.53** (1.77)	**6.39** (1.74)	**10.25** (1.69)	**7.16** (1.62)
MFSL	**10.06** (2.65)	**6.08** (1.98)	**12.02** (2.58)	**8.79** (1.85)
ORTHOK	**6.4** (1.88)	NA	**7.66** (1.32)	**4.26** (1.42)
PIR	**8.77** (3)	**5.32** (2.97)	**13.1** (2.82)	**8.06** (3.22)
PPSL	**10.99** (1.98)	**5.85** (1.98)	**11.49** (1.87)	**7.13** (1.85)
PSASCL	**12.4** (3.5)	NA	**9.06** (3.41)	NA
RGP	**12.97** (2.75)	**7.69** (2.36)	**16.29** (2.18)	**11.76** (1.6)
RLRL	**1.52** (0.7)	NA	**1.85** (0.55)	NA
RLRL+ORTHOK	NA	NA	**1.34** (0.77)	NA
UCSVL	**16.23** (1.11)	**10.19** (1.32)	**16.04** (1.79)	**11.56** (1.45)

Rebound effect assessment

- Rebound effect is defined as accelerated myopia progression 12 months after treatment cessation, measured either as change in SER (diopters) or in axial length (mm).
- Although less effective than MDA (0.1% to <0.5%) or HDA (≥0.5%) during the active treatment phase, a year after treatment cessation patients on LDA showed no evidence of a statistically or clinically meaningful rebound effect, while children previously treated with MDA or HDA progressed faster than children assigned to placebo (Figure 4). The rebound effect of RLRL, alone or in combination with ORTHOK, and that of LDA+ORTHOK, which were among the most effective treatment options, was not evaluated due to insufficient data.

Figure 4. Change in SER (left) or AL (right) 1 year after treatment cessation



Median posterior difference (95% CrI). In **blue**, statistically significant; In **grey**, not statistically significant. Reference treatment is control.

Network meta-regression

- The fixed effects univariate network meta-regressions indicated that the relative treatment effects were significantly **modified by geography, race, baseline risk or baseline SER**. In the random effects models, only baseline risk and baseline SER remained significant.
- **Baseline myopia progression rate**: Slower natural progression of childhood myopia (i.e. smaller absolute change from baseline in SER after 1 year on placebo by 1.0 D) is associated with a significant decrease in the relative effect on SER of -0.31 D at year 1. The impact on CFB in AL was not significant possibly due to aggregation bias.
- **Baseline SER**: One unit (1.0 D) increase in absolute baseline SER (indicating more severe myopia) was associated with a borderline significant decrease in the relative treatment effect on SER (-0.03 D at year 1). A unit increase in absolute baseline SER was not associated with a significant treatment effect on AL.
- **Race:** 1% increase in East Asian patients led to an increase in the relative treatment effect on SER (+0.06 D slower decline in SER vs control) and AL (-0.04 mm greater retardation of axial elongation vs control). The clinical plausibility of this effect is unclear.
- **Geography:** Western geography was associated with a borderline significant decrease in the relative effect on CFB in SER (-0.03 D) and on CFB in AL (+0.04 mm) vs Asian geography. The direction of the impact was consistent with that of race due to correlation between these variables.

CONCLUSIONS

- **LDA is a validated, evidence-based intervention for myopia control**, shown to significantly reduce pediatric myopia progression versus placebo or UCSVL
- Although NMA indicates that HDA and MDA are more effective in controlling myopia progression, **LDA offers a better balance between on-treatment efficacy and post-treatment rebound** effect compared to HDA or MDA.
- **LDA** was **consistently ranked higher than MFSCL, MFSL, PPSL, RGP or ARA in efficacy:** the relative differences did not reach statistical significance likely due to insufficient evidence and clinical/methodological heterogeneity among the included RCTs. Hence, LDA should be a favored option vis-à-vis optical interventions, even if its superiority over optical alternatives is not conclusively demonstrated.
- **Combining LDA with ORTHOK may enhance the overall efficacy of pediatric myopia control**: LDA+ORTHOK was ranked the third most effective treatment of 17 options after 1 year of treatment.

LIMITATIONS

- Although the NMA is based on a large evidence base, the quality of the RCTs ranged from low to moderate, with only six of 117 RCTs judged to be at low risk of bias. The efficacy of ORTHOK in attenuating SER decline may be inflated due to temporary flattening of the cornea after ORTHOK removal. The interaction between baseline age and treatment effect was not significant in the NMR possibly due to insufficient data. Safety could not be compared in the NMA due to scarce and inconsistent reporting in the RCTs.

Abbreviations: AL, axial length; ARA, adenosine receptor antagonists; CFB, change from baseline; CONT, control (Placebo, Single vision spectacles or Single vision soft contact lenses); CrI, credible interval; D, diopters; DIC, deviance information criterion; DOTSL; diffusion optics technology spectacle lenses; FE, fixed effects; HDA, high dose atropine; HTA, health technology assessment; ITC, indirect treatment comparison; LARISL, lenslet array integrated spectacle lenses; LDA, low-dose atropine; MDA, moderate dose atropine; MFSL, multifocal spectacle lenses; MFSCL, multifocal soft contact lenses; mm, millimeter; NA, not applicable; NMA, network meta-analysis; ORTHOK, orthokeratology lenses; PIR, pirenzepine; PPSL, peripheral plus spectacle lenses; PSASCL, positive spherical aberration soft contact lenses; RCT, randomized controlled trial; RE, random effects; RGP, rigid gas-permeable contact lenses; RLRL, Repeated low-intensity red light therapy; SD, standard deviation; SER, spherical equivalent refraction; SLR, systematic literature review; UCSVL, under-corrected single vision spectacles.

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