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3-year results of 0.01% and 0.1% loading dose atropine treatment including washout in Danish children with myopia: a placebo-controlled, randomised clinical trial

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ABSTRACT

Aim To examine the safety and efficacy of low-dose atropine (0.01% and 0.1% loading dose) after 2-year treatment and 1-year washout in 6-year-old to 12-year-old Danish children with myopia.

Methods Investigator-initiated, placebo-controlled, double-blind, randomised clinical trial. Of 124 screened children, 97 were randomised to receive 0.01% low-dose atropine for 24 months (0.01%) or 0.1% low-dose atropine for 6 months, then 0.01% for 18 months (0.1% loading dose) or placebo, followed by a 1-year washout. Altogether, 91 participants completed the study. The primary outcome was myopia progression (axial length (AL) and spherical equivalent refraction (SER)). Secondary outcomes were adverse events, ocular biometrical measurements and treatment responder eyes (myopia progression less than −0.50 diopters (D)). Constrained linear mixed models were constructed with individual eyes nested by participant ID, according to intention-to-treat. The responder analysis used Fisher's exact test. Significance levels were adjusted for multiple comparisons. Adjusted p values <0.05 were considered significant.

Results At 3 years, the mean AL was −0.06 mm (95% CI −0.18; 0.07) and −0.09 mm (95% CI −0.21; 0.04) less compared with placebo in the 0.1% loading dose group and 0.01% group. Mean SER was −0.02 D (95% CI −0.30; 0.26) less and 0.17 D (95% CI −0.11; 0.45) more compared with placebo in the 0.1% loading dose group and 0.01% group. There was no significant group difference in the responder eyes.

Conclusion There was no difference in myopia progression between groups following washout. A 6-month 0.1% loading dose did not improve efficacy compared with 0.01%. The 0.1% loading dose showed a rebound effect after dose switching.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Low-dose atropine is an effective intervention to reduce myopia progression in children with myopia, at least during active intervention.

WHAT THIS STUDY ADDS

⇒ Following a 1-year washout axial elongation was not statistically significantly different in the low-dose atropine groups compared with placebo. The 0.1% loading dose seemed to exhibit a rebound effect following dose switching.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Low-dose atropine is a safe and efficacious treatment, at least during active intervention. Low-dose atropine treatment seems relevant at least for more myopic individuals. To determine optimal dosing, more head-to-head comparisons of atropine concentrations in populations outside of Asia seem prudent.

INTRODUCTION

Myopia prevalence is increasing worldwide,[1] with some countries in Asia reporting youth prevalence above 70%.[2 3] In Denmark, adolescent myopia prevalence has been estimated to be 17.9%.[4] While high myopia (less than −6 diopters (D)) drastically increases the risk of myopia-related long-term complications and, ultimately, the risk of blindness,[5] even lower degrees of myopia have been associated with increased risk.[6]

Many myopia control methods are currently used to mitigate myopia progression and thereby the risk of long-term complications.[7–11] Of these, low-dose atropine eye drops have been confirmed to be moderately efficacious,[7 12–16] at least during active treatment. While active intervention with atropine eye drops shows a concentration-dependent efficacy gradient, the Atropine for the Treatment of Myopia (ATOM) 2 study found that 0.01% atropine ultimately performed better than higher concentrations. This was speculated to be due to better second-year efficacy and a lesser rebound effect following treatment cessation (washout).[17] Low-dose atropine exhibiting a ceiling effect could potentially explain their observation of better second-year performance of 0.01%, that is, 0.1% likely reached maximum concentration and efficacy earlier. Regarding rebound, few studies have examined myopia progression after washout, with conflicting results.[18–21] Intuitively, an optimal atropine treatment strategy would use a high initial

concentration to rapidly curb progression, followed by a concentration taper to mitigate the subsequent rebound effect.

This paper reports the efficacy and safety of low-dose atropine eye drop (0.01% vs 0.1% loading dose followed by 0.01%) treatment for 2 years, followed by a 1-year washout period in 6-year-old to 12-year-old Danish children with myopia. Our aim was to determine if treatment effects were sustained after washout and whether a loading dose was beneficial to the final outcome.

METHODS

Trial design

This study was an investigator-initiated, randomised, placebo-controlled study examining the efficacy and safety of low-dose atropine after a 2-year treatment and subsequently a 1-year washout. Participants were allocated 1:1:1 to 0.01% for 2 years versus a 0.1% loading dose for 6 months followed by 0.01% for 18 months versus placebo, respectively.

Participants

Danish children with myopia were referred from optometrists and ophthalmologists across Denmark. Screening, baseline and follow-up examinations were performed at the Department of Ophthalmology at Copenhagen University Hospital, Rigshospitalet, University Hospital of Southern Denmark, Vejle, and Aarhus University Hospital, respectively. Children between 6 and 9 years of age with at least one negative spherical diopter in one eye and children between 9 and 12 years of age with at least two negative spherical diopters in one eye were included. This age-related distinction in myopia degree was chosen to ensure active myopia progression in participants. We excluded children who had previously undergone myopia control methods, children with myopia related to other retinal dystrophies, collagen syndromes, other ocular pathologies (such as strabismus), previous eye surgery, serious systemic disorders or children unable to comply with eye examinations. For more detailed information on inclusion criteria, see our published interim analysis.[22]

Intervention

Eligible participants were randomised to either 0.01% low-dose atropine for 24 months (0.01%), 0.1% loading dose for 6 months followed by 18 months of 0.01% (0.1% loading dose) or placebo (placebo). The intervention was followed by a 1-year washout for all groups. The intervention was applied by the participant's parents administering one drop in each eye before bedtime. The administration was documented by parents via handout checklists.

Outcomes

The primary outcome was non-cycloplegic axial length (AL) and cycloplegic spherical equivalent refraction (SER) changes following treatment and a 1-year washout. Secondary outcomes were treatment responder eyes (number of eyes in each intervention group where myopia had not progressed by more than −0.50 D from baseline at the first-, second- and third-year visit), adverse events and reactions, near and far best-corrected visual acuity (BCVA), intraocular pressure (IOP), accommodation amplitude, photopic and mesopic pupil diameters and ocular biometrical measurements during and after washout.

Sample size, randomisation and allocation concealment

The power calculation before the study commencement was performed with an expectation of detecting a 50% difference in SER change between the intervention groups and placebo based on previously published SER progression rates in Danish adolescents.[23] Detecting a 50% SER progression difference after 3 years with a significance level of 0.05 required a sample size of a minimum of 21 in each treatment arm. Additional participants were recruited to account for the unknown effect size in Danish children, potential dropout and the length of the study. The randomisation procedure was performed by a computer algorithm in-built in the electronic clinical report form, allocating participants 1:1:1 to the 0.1% loading dose, 0.01% or placebo group. Randomisation status was masked from parents, participants and trial staff to ensure allocation concealment. In addition, statistical analyses were performed blinded to randomisation status.

Examinations

Autorefraction (Right group, Retinomax K-plus 3, Tokyo, Japan) in cycloplegia was used to determine SER. Cycloplegia was achieved via cyclopentolate 1% eye drops (Minims cyclopentolate hydrochloride 1%, Bausch and Lomb Nordic AB, Stockholm, Sweden) administered ×2 in each eye, divided by a 5-min wait and then a 30-min break to achieve cycloplegia. The SER was calculated as half the cylindrical diopters added to the spherical diopters. Push-plus subjective refraction was performed with the current prescription and autorefraction as starting points. A HOTV chart (Precision Vision, La Salle, Illinois, USA) was used to determine near (40 cm) and far (4 m) visual acuity while using the best-corrected prescription. A Royal Air Force near-point ruler was used to determine the amplitude of accommodation. The iridocorneal angle was determined via Scheimpflug imaging (Oculus GmbH, Pentacam HR System, Wetzlar, Germany). The IOP was determined as the mean of five measurements with a rebound tonometer (iCare Finland Oy, iCare, Vantaa, Finland). Photopic (300 lux) and mesopic (4 lux) pupil diameters were determined as the mean of five measurements with a pupillometric device (DP-2000 Pupillometer, NeurOptics, California, USA). The AL, anterior chamber depth (ACD), central corneal thickness (CCT) and lens thickness (LT) were measured via optical biometry (IOLMaster 700, Carl Zeiss AG, Oberkochen, Germany). Potential side effects, including eye irritation/redness on application, difficulties with near or far vision, dilated pupils, photophobia or other (including anticholinergic side effects), were documented by an examiner at each visit.

Statistical methods

Linear mixed models with an unstructured covariance pattern to account for variance heterogeneity over time and correlation between same-site measurements were constructed with treatment and study site as fixed effects. Individual eyes as a binary variable nested in participant ID (to use both eyes in the analysis) were included as a random effect. The models were constrained to assume the same mean baseline value for all groups. The treatment responder analysis used Fisher's exact test to determine whether there was a significant difference in the number of responder eyes between the intervention groups and placebo at 1-year intervals. Analyses were performed according to intention-to-treat. The R statistical programme V.4.2.0 (R Programme for Statistical Computing, Vienna, Austria)[24] and the LMMstar package[25] were used for the statistical analysis. Multiple comparisons adjustment was performed using the false discovery

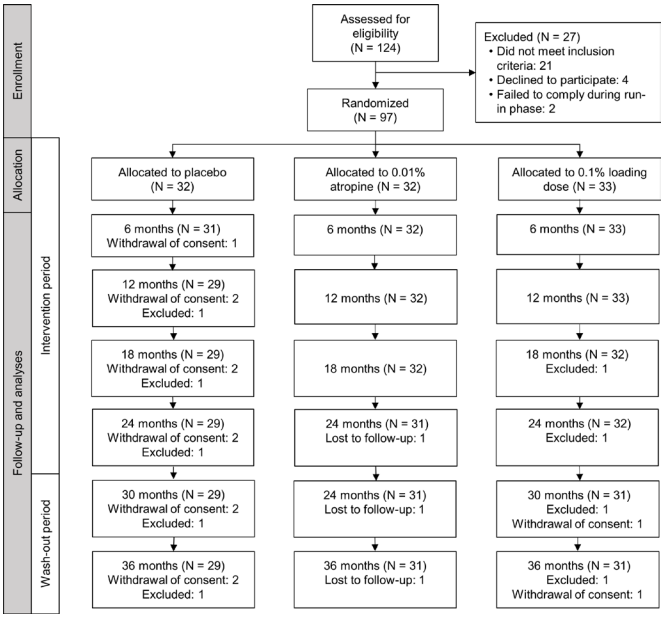

Figure 1 Consolidated standards of reporting flow diagram of the trial. 0.01%, participants who received 0.01% for the first 2 years; 0.1% loading dose, participants who received 0.1% for the first 6 months and then 0.01% for the subsequent 18 months before washout; placebo, participants who received placebo during the 2 years of active intervention; N, number of participants; washout period, the period following active intervention where no intervention was administered.

rate.[26] Adjusted p values <0.05 were considered statistically significant.

RESULTS

We screened 124 candidates for participation. 16 candidates did not meet inclusion criteria, 6 declined further participation after the screening, 3 could not comply with the examinations, and 2 could not comply with the eye drop regimen, which was tested with lubricating eye drops prior to randomisation. Therefore, 97 participants were randomised to the three intervention groups (figure 1). Recruitment and follow-up took place between May 2019 and May 2024. The mean age of included participants was 9.4 years (range 6–12), 43% were male, the mean AL was 24.6 mm (SD 0.84), and the mean SER was −2.99 D (SD 1.27). Ethnically, 82 (84%) participants had white ethnicity, 3 (3%) had Middle Eastern ethnicity, 2 (2%) had Asian ethnicity, 1 (1%) had African ethnicity, and 9 (10%) had mixed ethnicity. Six participants (6%) dropped out during the study. Of these, three withdrew consent, one participant emigrated, one participant wanted to try another myopia control method, and one participant was lost to follow-up after the 18-month visit. In total, 91 participants (94%) completed all visits.

AL and SER changes after 1 year of washout

3-year mean AL was 25.28 mm (95% CI 25.06; 25.50), 25.25 mm (95% CI 25.03; 25.47) mm and 25.33 mm (95% CI 25.11; 25.56) in the 0.1% loading dose, 0.01% and placebo group, respectively. The mean AL change from baseline after the third-year washout was −0.06 mm (95% CI −0.18; 0.07) and −0.09 mm (95% CI −0.21; 0.04) less in the 0.1% loading dose group and 0.01% group, respectively, compared with placebo, which was not statistically significant (table 1 and figure 2).

3-year mean SER was −4.45 D (95% CI −4.84; −4.06), –4.26 D (95% CI −4.65; −3.87) and −4.43 D (95% CI −4.83; −4.03) in the 0.1% loading dose, 0.01% and placebo groups, respectively. The mean SER change from baseline after the third-year washout was −0.02 D (95% CI −0.30; 0.26) and 0.17 D (95% CI −0.11; 0.45) less in the 0.1% loading dose group and 0.01% group, respectively, compared with placebo, which was not statistically significant (table 1 and figure 3).

Treatment responder analysis after 12 months, 24 months and washout

There was no statistically significant difference in treatment responder eye proportions between groups at any of the time points (table 2). Percentages of eyes more myopic than less than −5 D are also shown in table 2.

Corneal thickness and curvature, ACD, iridocorneal angle and LT after washout

The CCT, K1 and K2, ACD, iridocorneal angle and LT measured after the washout phase were similar to the values obtained at baseline and comparable between intervention groups (online supplemental table 1).

Safety measures and reported events during washout

The parent-administered handout leaflet indicated excellent treatment adherence (6/7 days per week for all participants). Near and far BCVA, mesopic and photopic pupil diameters and accommodation amplitude were similar to baseline and comparable between groups after washout (table 1). The IOP had increased compared with baseline after washout but was comparable between groups and still within normal limits. In total, seven adverse events were reported during the washout phase (table 3). There were no serious adverse events reported during the washout phase of the study.

DISCUSSION

This paper reports the safety and efficacy of low-dose atropine eye drops (0.01% and 0.1% loading dose) after 2 years of intervention followed by a 1-year washout in Danish children with myopia. While we observed that participants receiving 0.01% had marginally less progression than those receiving the 0.1% loading dose or placebo, the difference was not statistically or clinically significant after washout. We observed a few more responder eyes in the 0.01% group compared with placebo, but the difference was not statistically significant.

Low-dose atropines moderate effect observed in our trial after 2 years of treatment with 0.01%,[16] and the lack of effect and statistical significance of 0.01% after washout, could be due to 0.01% being too low a concentration to achieve a marked effect during longer treatment periods in Danish children with myopia or because the effect cannot be sustained following treatment cessation. For Asian children with myopia, Yam *et al* have found that 0.05% had a superior efficacy compared with 0.01% in preventing incident myopia and offered the best compromise between treatment effects and side effects for this population.[27] In contrast, while Zadnik *et al* recently found reduced axial elongation in both their 0.02% and 0.01% groups of US children with myopia after 3 years of intervention,[14] only their 0.01% group had a statistically significant amount of responders to the treatment, and counterintuitively, not their 0.02%

Table 1 Linear mixed model mean effect estimates of ophthalmic parameters after 2 years of treatment during the washout period

Group time point	Placebo	0.1% loading dose	0.01%
Axial length, mm			
Baseline	24.60 (24.42; 24.78)		
30 mo	25.26 (25.04; 25.47)	−0.07 (−0.18; 0.04)	−0.09 (−0.20; 0.018)
30-mo adjusted-p		*0.82*	*0.76*
36 mo	25.33 (25.11; 25.56)	−0.06 (−0.18; 0.07)	−0.09 (−0.21; 0.04)
36-mo adjusted-p		*0.86*	*0.78*
Spherical equivalent refraction, diopters			
Baseline	−2.99 (−3.26; −2.71)		
30 mo	−4.27 (−4.64; −3.91)	0.03 (−0.20; 0.27)	0.07 (−0.17; 0.30)
30-mo adjusted-p		*0.94*	*0.86*
36 mo	−4.43 (−4.83; −4.03)	−0.02 (−0.30; 0.26)	0.17 (−0.11; 0.45)
36-mo adjusted-p		*0.94*	*0.82*
Intraocular pressure, mm Hg			
Baseline	16.2 (15.5; 16.9)		
30 mo	17.7 (16.7; 18.6)	0.3 (−0.8; 1.4)	0.3 (−0.8; 1.4)
30-mo adjusted-p		*0.86*	*0.86*
36 mo	17.8 (16.8; 18.8)	−0.9 (−2.0; 0.2)	−0.9 (−2.0; 0.2)
36-mo adjusted-p		*0.76*	*0.76*
Distance BCVA, LogMAR			
Baseline	−0.12 (−0.13; −0.10)		
30 mo	−0.11 (−0.13; −0.09)	−0.01 (−0.03; 0.02)	−0.01 (−0.03; 0.02)
30-mo adjusted-p		*0.86*	*0.86*
36 mo	−0.11 (−0.13; −0.09)	−0.01 (−0.03; 0.01)	−0.02 (−0.04; 0.00)
36-mo adjusted-p		*0.86*	*0.76*
Near BCVA, LogMAR			
Baseline	−0.08 (−0.09; −0.06)		
30 mo	−0.08 (−0.10; −0.05)	−0.01 (−0.03; 0.02)	0.01 (−0.02; 0.04)
30-mo adjusted-p		*0.86*	*0.86*
36 mo	−0.08 (−0.10; −0.05)	0.00 (−0.03; 0.02)	0.00 (−0.03; 0.02)
36-mo adjusted-p		*0.94*	*0.94*
Accommodation amplitude, diopters			
Baseline	16.4 (15.6; 17.2)		
30 mo	17.2 (16.1; 18.2)	0.3 (−0.8; 1.5)	−0.4 (−1.5; 0.8)
30-mo adjusted-p		*0.86*	*0.86*
36 mo	16.3 (15.3; 17.3)	0.0 (−1.2; 1.0)	0.0 (−1.1; 1.1)
36-mo adjusted-p		*0.94*	*0.99*
Mesopic pupil diameter, mm			
Baseline	4.47 (4.25; 4.69)		
30 mo	4.41 (4.17; 4.64)	0.00 (−0.26; 0.25)	−0.02 (−0.27; 0.23)
30-mo adjusted-p		*0.99*	*0.94*
36 mo	4.37 (4.10; 4.64)	−0.11 (−0.41; 0.20)	−0.04 (−0.35; 0.27)
36-mo adjusted-p		*0.86*	*0.94*
Photopic pupil diameter, mm			
Baseline	2.97 (2.81; 3.12)		
30 mo	2.79 (2.68; 2.91)	0.06 (−0.07; 0.19)	−0.01 (−0.14; 0.12)
36-mo adjusted-p		*0.86*	*0.94*
36-mo	2.80 (2.59; 3.02)	0.07 (−0.19; 0.32)	0.05 (−0.20; 0.31)
36-mo adjusted-p		*0.86*	*0.88*

Effect estimates presented as total for the placebo group and differences from the placebo group for the intervention groups (0.1% loading dose and 0.01% groups).
Adjusted significance levels are reported for the visits during the washout period (30 and 36 months) after adjusting for the false discovery rate.
0.1% loading dose, participants who received a 0.1% loading dose the first 6 months of intervention and then 0.01% for the remaining 18 months of intervention; 0.01%, participants who received 0.01% for the full 2 years of the intervention; placebo, participants who received placebo during the 2 years of active intervention.
mo, months; SER, spherical equivalent refraction.

group, highlighting that the optimal dose for myopic populations outside of Asia as of yet still seems uncertain. Regarding the sustainment of effect after washout, the ATOM2 study found that 0.01% had superior efficacy compared with higher concentrations after 1 year of washout in Asian children with myopia.[7] However, a 10-year follow-up analysis on the ATOM2

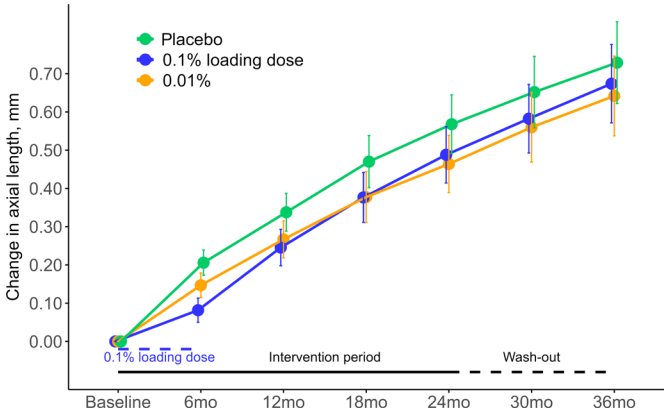

Figure 2 Changes in AL during the 3-year study period. 0.1% loading dose, participants who received 0.1% loading dose during the first 6 months of intervention and then 0.01% for the remaining 18 months of intervention; 0.01%, participants who received 0.01% for the full 2 years of the intervention; placebo, participants who received placebo during the 2 years of active intervention; washout, a period where intervention was stopped to determine efficacy after treatment cessation.

participants found no differences in final refractive error between the atropine groups.[20] It must be noted that this follow-up study had moderate participation for the ATOM2 follow-up analysis (39.5%), endangering the risk of selection bias. The ATOM2 follow-up analysis also did not employ a placebo group, therefore lacking comparison to non-treated individuals. Retainment of a clinically significant effect after 1 year of treatment cessation of 0.01% atropine in children of white ethnicity seems unlikely, but more studies evaluating the long-term effect following treatment cessation are welcomed.

The mean 2-year axial elongation was 0.57 mm in our placebo group. This was comparatively faster than that observed in the trial from the Paediatric Eye Disease Investigator Group (PEDIS, 0.45 mm),[15] the Western Australia ATOM (WA-ATOM) study (0.38 mm)[28] and the Myopia Outcome Study of Atropine in Children (MOSAIC, 0.40 mm).[13] Our faster axial elongation rate

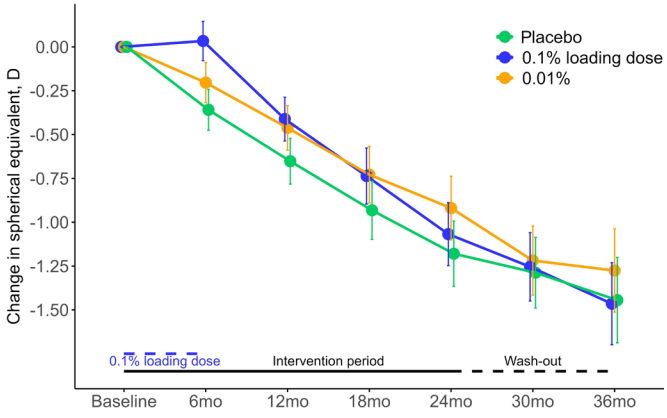

Figure 3 Changes in spherical equivalent refraction during the 3-year study period. 0.1% loading dose, participants who received 0.1% loading dose during the first 6 months of intervention and then 0.01% for the remaining 18 months of intervention; 0.01%, participants who received 0.01% for the full 2 years of the intervention; D, diopters; placebo, participants who received placebo during the 2 years of active intervention; washout, period where intervention was stopped to determine efficacy after treatment cessation.

could partly be explained by ethnic differences between studies, given our larger proportion of children of white ethnicity (85% vs PEDIS: 46%; WA-ATOM: 50%), although the proportion was comparable to MOSAIC (80.8%). A more likely explanation for our faster axial elongation rate, therefore, is the comparably younger mean age of our participants (9.4±1.7 years vs PEDIS: 10.1±1.8 years; WA-ATOM: 12.2±2.5 years; MOSAIC: 11.8±2.2 years), which might have enabled recruitment of more actively progressing children, since myopia progression is thought to occur at a faster rate between 6 and 10 years of age,[29] or the fact that we opted for 9-year-old to 12-year-old children to have a higher myopia degree (two negative spherical diopters or more) to ensure an active progression in older participants.

Atropine eye drop treatment cessation is speculated to be followed by temporarily increased myopia progression, that is, a 'rebound effect', but few studies have examined this.[18–21] Of note, Lee *et al* recently found more myopia progression following washout in their 0.01% group compared with the placebo, although it should be considered that the placebo group experienced markedly more dropout (≈25%), and placebo participants were on average 1 year older, which could confound their findings due to the age-related stabilisation of myopia associated with the late teen years.[19] In contrast, Hieda *et al* found that 0.01% was not associated with a rebound effect during the 1-year washout, but their follow-up analysis had a small participation rate (30%).[21] The ATOM2 study speculated that dose tapering might mitigate this rebound,[7] which was our reason for including a 0.1% loading dose. However, as we observed, the effect size for our 0.01% group began to catch up to the 0.1% loading dose group at the 12-month visit (6 months after the 0.1% loading dose was reduced to 0.01%), and AL in the 0.01% group was statistically significantly reduced compared with placebo at the 2-year visit, in contrast to the non-significant effect estimate in the 0.1% loading dose group.[16] Likewise, considering that the observed ultimate effect size was larger in the 0.01% group compared with the 0.1% loading dose group at the final visit following washout, and the comparison between 0.01% and placebo was still statistically insignificant, it follows that statistically, we found no difference in effect size between intervention groups following washout. Consequently, even though intuitively a loading dose seems prudent, we found that starting at a 10 times higher concentration then tapering might predispose to a higher final refraction and seems unlikely to lead to superior efficacy after washout. Both the ATOM2 and the Low-Concentration Atropine for Myopia Progression study speculated that 0.01% achieved superior efficacy in the ATOM2 study because of a cumulative effect, that is, lower dosages of atropine might only reach their concentration threshold and, thereby, full efficacy, during the second year of treatment.[7 12] The fact that the effect in our 0.1% loading dose group lost statistical significance compared with placebo after dose switching (at the 6-month visit), while the 0.01% retained its moderate efficacy for the full 2-year intervention, indicates that a rebound effect could have occurred in the 0.1% low-dose atropine group in this period. We performed a post hoc analysis (t-test) comparing the eyes of children younger and older than 10 years in the 0.1% loading group to see whether an age-specific difference in rebound effect was present; however, this seems not to be the case (p=0.34). The superior effect of 0.01% following dose switching at 6 months could also be due to low-dose atropine exhibiting a ceiling effect, that is, after a certain concentration threshold, further increasing the concentration would only have an incremental added effect. To determine optimal treatment concentration, we recommend that future studies should

Table 2 Treatment responder eyes per group by visit

Treatment responder eyes per group by visit			
Group/visit	**First year**	**Second year**	**Third year**
0.1% loading dose group responders	39 (61%), Adjusted-p = 0.86*	19 (31%), Adjusted-p = 0.88*	10 (18%), Adjusted-p = 1.00*
0.01% group responders	40 (69%), Adjusted-p = 0.76*	22 (38%), Adjusted-p = 0.82*	12 (21%), Adjusted-p = 0.87*
Placebo group responders	27 (54%)	15 (26%)	9 (17%)
Eyes less than −5 D per group by visit			
Group/visit		**Second year**	**Third year**
0.1% loading dose group		13 (21%)	15 (24%)
0.01% group		8 (14%)	11 (18%)
Placebo group		12 (21%)	13 (23%)

0.1% loading dose, participants who received 0.1% loading dose the first 6 months of intervention and then 0.01% for the remaining 18 months of intervention.
0.01% loading dose, participants that received 0.01% for the full 2 years of the intervention.
Responders, eyes that experienced less than 0.50 D progression from baseline to the given visit.
*Compared to placebo at the given time point.

examine this potential ceiling effect by successively increasing atropine concentration until maximum effect is reached, while at the same time staying at a concentration minimising unwanted pupil- and accommodation-related side effects.[7]

To ensure fewer patients end up experiencing myopia-related long-term complications, it might be as relevant to determine treatment responders as it is to examine the final effect size. Zadnik *et al* found that after 3 years of treatment, the responder

Table 3 Adverse events and reactions reported before and during the 1-year washout phase

Group	Event	24 mo	30 mo	36 mo
0.1% loading dose	Total events, N/total N (%)	5/32 (16%)	2/31 (6%)	2/31 (6%)
	Eye redness/irritation, N/total N (%)	1/32 (3%)	0/31 (0%)	1/31 (3%)
	Photophobia, N/total N (%)	1/32 (3%)	0/31 (0%)	0/31 (0%)
	Blurred near vision, N/total N (%)	1/32 (3%)	0/31 (0%)	0/31 (0%)
	Blurred distance vision, N/total N (%)	0/32 (0%)	0/31 (0%)	0/31 (0%)
	Other, N/total N (%)	2/32 (6%)	2/31 (6%)	1/31 (3%)
	Dilated pupils, N/total N (%)	0/32 (0%)	0/31 (0%)	0/31 (0%)
0.01%	Total events, N/total N (%)	1/31 (3%)	2/31 (6%)	0/31 (0%
	Eye redness/irritation, N/total N (%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
	Photophobia, N/total N (%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
	Blurred near vision, N/total N (%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
	Blurred distance vision, N/total N (%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
	Other, N/total N (%)	1/31 (3%)	2/31 (6%)	0/31 (0%)
	Dilated pupils, N/total N (%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
Placebo	Total events, N/total N (%)	3/29 (10%)	1/29 (3%)	0/29 (0%)
	Eye redness/irritation, N/total N (%)	1/29 (3%)	0/29 (0%)	0/29 (0%)
	Photophobia, N/total N (%)	1/29 (3%)	0/29 (0%)	0/29 (0%)
	Blurred near vision, N/total N (%)	0/29 (0%)	0/29 (0%)	0/29 (0%)
	Blurred distance vision, N/total N (%)	0/29 (0%)	0/29 (0%)	0/29 (0%)
	Other, N/total N (%)	1/29 (3%)	1/29 (3%)	0/29 (0%)
	Dilated pupils, N/total N (%)	0/29 (0%)	0/29 (0%)	0/29 (0%)

total N, total number of participants in the given group; N, number of adverse events.

percentages (myopia progression of less than −0.50 D) were 17.5%, 28.5% and 22.1%, respectively, in their placebo, 0.01% and 0.02% groups.[14] In comparison, we observed 38% and 26% responders, respectively, in the 0.01% and placebo groups after a 2-year intervention. Considering their 1-year longer intervention, the responder percentages between studies seem similar. Notably, they found the most responders in their 0.01% group, not their 0.02% group, similar to our observation of the most responders in our 0.01% group, although the difference was not statistically significant from placebo. Ultimately, we speculate that low-dose atropines comparatively modest treatment effects observed in settings outside of Asia[13–16] cannot necessarily be ascribed to inefficaciousness but could also be due to 0.01% being too low a concentration. Conversely, as determined by this study, 0.1% seems too high, as it triggers a marked rebound on dose reduction. We recommend more head-to-head comparisons of atropine concentrations (including 0.05% as recommended by Yam *et al*[12 27]) to determine effectiveness for myopic populations outside of Asia.

When determining treatment effect, it is important to consider if the treatment was used as prescribed. We found that photopic and mesopic pupil diameters were increased in both intervention groups during the first year, indicating the drops had been used.[22] Administration documented by parents via a handout paper leaflet also showed excellent treatment adherence. This agrees with other low-dose atropine studies, which also report excellent treatment adherence.[12 14 15 30] Trial strengths include the randomised setup and the low dropout rate (6%), reducing the risk of selection bias. More head-to-head concentration comparisons would have been ideal but were not feasible for this trial. Our study was powered to detect a 3-year SER difference of 50% or more, given an expectation of −1 D progression per year, based on a previously published prospective study on SER progression rates in Danish adolescents.[23] Ultimately, however, this study documented a yearly SER progression of approximately 0.5 D, potentially making this study underpowered to detect group differences below a 50% difference threshold. The relatively modest sample size of our study might therefore have impaired our ability to detect a potential, although small, retained effect of the interventions following washout. While such a retained potential effect of 0.01% might have been shown to be statistically significant given a larger sample size, the clinical significance given the effect size would be debatable. Future power calculations would preferably be based on AL progression, such as in our placebo group, since AL, not SER, is the better predictor of myopia-related long-term complications. Ideally, treatment would have continued until the more rapid myopia progression observed during youth would have flattened out.[31] This increased myopia progression is thought to decelerate by age 12.[32] Considering that the mean age of our participants was 9.4 years at baseline, another year of active intervention might have been warranted, although treatment duration was limited by the inherent constraints of a randomised controlled trial. Another limitation of this study is that it would have been ideal to explore other potential factors affecting myopia progression, such as parental myopia, outdoor activity and near work.

In conclusion, there was no difference in myopia progression or treatment responders between the intervention groups and placebo following washout. A 0.1% loading dose for 6 months tapered to 0.01% for the remainder of the intervention did not improve treatment efficacy following washout compared with 0.01% mono-treatment. The 0.1% loading dose seemed to exhibit a rebound effect following dose switching at 6 months. More head-to-head comparisons of atropine concentrations in populations outside of Asia seem prudent. Future studies should examine whether atropine exhibits a ceiling effect by consecutively increasing concentration.

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Contributors Study conception and design: AH-H, NJ, FM, TB and LK; methodology: AH-H, NJ, FM, TB and LK; acquisition and collection of data: NH, AH-H, FM, TB, DL, NJ and LK; analysis and interpretation of results: NH, AH-H, FM, TB, DL, NJ and LK; drafting of the manuscript: NH; manuscript contributions and final approval: NH, AH-H, FM, TB, DL, NJ and LK. All authors are guarantors of this work.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. This study adhered to the declaration of Helsinki. Trial approval was obtained from the Danish Medicines Agency (reference number: 2018040088), the Danish Data Protection Agency via the Capital Region of Denmark (reference: P-2022-85) and the Committees on Health Research Ethics in the Capital Region of Denmark (reference number: H-18043987). The trial was registered in the European Clinical Trials Database (EudraCT, 2018-001286-16) and at clinicaltrials.gov (NCT03911271) prior to study commencement. Good Clinical Practice (GCP) was ensured by monitoring via the GCP units at the individual hospitals. Participants gave informed consent to participate in the study before taking part.

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