AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Five-Year Clinical Trial on Atropine for the Treatment of Myopia 2

Myopia Control with Atropine 0.01% Eyedrops

Audrey Chia, FRANZCO, PhD,[1,2] *Qing-Shu Lu, PhD,*[3,4] *Donald Tan, FRCS, FRCOphth*[1,2,4,5]

Purpose: To compare the safety and efficacy of different concentrations of atropine eyedrops in controlling myopia progression over 5 years.

Design: Randomized, double-masked clinical trial.

Participants: A total of 400 children originally randomized to receive atropine 0.5%, 0.1%, or 0.01% once daily in both eyes in a 2:2:1 ratio.

Methods: Children received atropine for 24 months (phase 1), after which medication was stopped for 12 months (phase 2). Children who had myopia progression (≥ -0.50 diopters [D] in at least 1 eye) during phase 2 were restarted on atropine 0.01% for a further 24 months (phase 3).

Main Outcome Measures: Change in spherical equivalent and axial length over 5 years.

Results: There was a dose-related response in phase 1 with a greater effect in higher doses, but an inverse dose-related increase in myopia during phase 2 (washout), resulting in atropine 0.01% being most effective in reducing myopia progression at 3 years. Some 24%, 59%, and 68% of children originally in the atropine 0.01%, 0.1%, and 0.5% groups, respectively, who progressed in phase 2 were restarted on atropine 0.01%. Younger children and those with greater myopic progression in year 1 were more likely to require re-treatment. The lower myopia progression in the 0.01% group persisted during phase 3, with overall myopia progression and change in axial elongation at the end of 5 years being lowest in this group (-1.38 ± 0.98 D; 0.75 ± 0.48 mm) compared with the 0.1% (-1.83 ± 1.16 D, $P = 0.003$; 0.85 ± 0.53 mm, $P = 0.144$) and 0.5% (-1.98 ± 1.10 D, $P < 0.001$; 0.87 ± 0.49 mm, $P = 0.075$) groups. Atropine 0.01% also caused minimal pupil dilation (0.8 mm), minimal loss of accommodation (2–3 D), and no near visual loss compared with higher doses.

Conclusions: Over 5 years, atropine 0.01% eyedrops were more effective in slowing myopia progression with less visual side effects compared with higher doses of atropine. *Ophthalmology 2016;123:391-399 © 2016 by the American Academy of Ophthalmology.*

See Editorial on page 232.

Several studies have shown that atropine eyedrops are effective in slowing myopia progression in young children.[1–19] In our past Atropine for the Treatment of Myopia (ATOM) 1 and 2 (phases 1 and 2) clinical trials, we demonstrated a dose-related response to atropine, with higher doses inhibiting myopia progression to a slightly greater degree than lower doses, although the myopia progression of −0.49 diopters (D), −0.38 D, and −0.30 D in the atropine 0.01%, 0.1%, and 0.5% groups, respectively, were not significantly different at 24 months.[16,19] However, when atropine was stopped for 12 months after 24 months of treatment (phase 2 of ATOM2), there was a rapid increase in myopia in children originally treated with higher concentrations of atropine, whereas those receiving the lowest concentration of 0.01% showed minimal change.[18,20] This resulted in myopia progression being significantly lower in children previously assigned to the 0.01% group (−0.72 D) at 36 months compared with that in the 0.1% (−1.04 D) and 0.5% (−1.15 D) groups. In addition, the lowest dose also caused less photopic pupil dilation (0.74 mm, compared with 2.25 and 3.11 mm in the 0.1% and 0.5% groups, respectively) and no clinically significant loss in accommodation or near visual acuity (4.6 D, compared with 10.1 and 11.8 D in the 0.1% and 0.5% groups, respectively).[20]

Although proven effective and safe in the short-term, there was concern about the long-term effectiveness of atropine, particularly in children who experienced an increase in myopia after atropine was stopped. In the final phase (phase 3), spanning the fourth and fifth years of the ATOM2 study, children who continued to progress (>0.5 D/year) during phase 2 (the washout year) were re-treated with atropine 0.01%. The aim of this study was to evaluate the efficacy and safety of atropine over this last phase and the entire 5-year study period.

Methods

In phase 1 of the ATOM2 study (treatment phase), 400 Asian children (aged 6–12 years) with myopia of −2.00 D or worse in each eye were randomized to receive atropine 0.01%, 0.1%, and

http://dx.doi.org/10.1016/j.ophtha.2015.07.004
ISSN 0161-6420/15

0.5% once nightly in both eyes for 2 years. Children were assigned to treatment in a 1:2:2 ratio, stratified by 6 gender and age strata. In phase 2 (washout phase), atropine was stopped and children were monitored for 12 months. In phase 3 (re-treatment phase), children who exhibited myopia progression of −0.50 D or more in at least 1 eye during the washout phase were restarted on atropine 0.01% for a further 24 months.

Written informed consent was obtained from parents and verbal assent was obtained from children before randomization. The investigators, study team performing the ocular measurements, parents, and children were masked to an initial dose of atropine throughout the entire 5-year study, and the study team was also blinded to whether or not children were restarted on atropine during the last phase of the study.

After assessment at a screening visit, children were reassessed again after they had been receiving atropine for 2 weeks (baseline visit). Children were then reviewed every 4 months during phase 1, at 26, 32, and 36 months during phase 2, and all children, including those who were not restarted atropine treatment, were reviewed every 6 months during phase 3 and then again in 2 months after all medication had been stopped.

At each visit, cycloplegic autorefraction, axial length (AL), mesopic and photopic pupil size, accommodation and distance, and near logarithm of the minimum angle of resolution visual acuity were measured.[19,20] Cycloplegia was achieved using 3 drops of cyclopentolate 1% administered 5 minutes apart, and cycloplegic autorefraction was measured, 30 minutes after the last drop, using a Canon RK-F1 autorefractor (Canon Inc. Ltd., Tochigiken, Japan). Five readings, all of which were within 0.25 D apart, were averaged. Spherical equivalent was calculated as the sphere plus half cylindrical power. Axial length was obtained using the Zeiss IOL Master (Carl Zeiss Meditec Inc., Dublin, CA). Five readings, all within 0.05 mm or less, were averaged. The photopic pupil size was measured using the Neuroptics pupillometer (Neuroptics Inc., Irvine, CA) at 300 lux of luminance. Accommodation was measured using the Royal Air Force rule while the subjects used their best-corrected distance spectacles. Distance and near vision were measured using logarithm of the minimum angle of resolution Early Treatment Diabetic Retinopathy Study charts.

The primary outcome was progression of myopia, defined as change in spherical equivalent over phase 3 and the entire 5-year study period. The secondary outcome was change in AL. Other study variables include changes in photopic pupil size, accommodation, and distance/near visual acuity.

The study was conducted according to the tenets of the Declaration of Helsinki. Ethics approval was obtained from the Singapore Eye Research Institute Review Board, and the study was registered with the ClinicalTrial.govwebsite (registration no: NTC00371124).

Statistical Analysis

All analyses were based on an intention-to-treat principle and performed using the statistical software SASv9.3 (SAS Inc., Cary, NC). Data were summarized by initial atropine treatment group in the re-treated and untreated children at the phase 3 stage. For person-level data such as gender, the Fisher exact test was used to test for the difference in proportion of children between groups, and analysis of variance was used for the difference in means between groups. Data of ocular parameters from both eyes were pooled in a combined analysis using the Huber−White robust standard errors to allow for correlation between eyes within a person.[21] Although P values (without adjustment for multiple comparison) were obtained for both the global null hypothesis of no difference among treatment groups and the pairwise comparison, interpretation only began with considering the global null hypothesis to prevent inflation of type I error rate.

Results

Among the 400 children enrolled in the study, 44 were lost in phase 1 and 11 were lost in phase 2, with 345 (86%) continuing to phase 3 (Fig 1). Children still in the study at the start of phase 3 were more myopic at baseline but had less myopic progression over the first year compared with children who were lost to follow-up (Table 1). The majority of the children (91%) were of ethnic Chinese origin.

Of the 345 children, 192 (56%) were restarted on atropine 0.01% because they had progressed 0.5 D or more during the preceding phase 2 washout year; this included 17 of 70 children (24%) in the 0.01% group, 82 of 139 children (59%) in the 0.1% group, and 93 of 136 children (68%) in the 0.5% group (Fig 2). Compared with children who were not restarted on atropine, those restarted on treatment were younger, had less myopia and shorter AL at baseline, but had greater myopia progression and change in AL during the first year of the study (Table 1). Multivariate analysis revealed that younger age and assignment to higher initial atropine dose predisposed children to greater myopic progression in phase 2 (Table 2) and thus more likely to be re-treated with atropine 0.01% in phase 3.

Myopia Progression

Children who required re-treatment had higher rates of myopia progression during the first 24 months (phase 1) and in the washout phase (phase 2) compared with those who did not require re-treatment (Table 3). In the re-treated children, mean annual myopia progression during phase 3 (−0.38 to −0.52 D) was lower than in the preceding phase 2 period (−0.62 to −1.09 D) in all 3 atropine groups, but higher than those who did not require re-treatment (−0.30 to −0.38 D) (Table 3). The overall mean myopia progression in phase 3 was −0.69±0.46 D, −0.81±0.57 D, and −0.84±0.61 D in the atropine 0.01%, 0.1%, and 0.5% groups, respectively ($P = 0.09$) (Fig 3). In contrast, the mean myopia progression over the entire 5 years was less in the 0.01% group (−1.38±0.98 D) than in the 0.1% (−1.83±1.16 D, $P = 0.003$) and 0.5% (−1.98±1.10 D, $P < 0.001$) groups.

The rate of myopic progression in children restarted on atropine slowed in phase 3. The mean increase in myopia over the fourth and fifth years (−0.86±0.56 D in 0.01% group, −0.87±0.59 D in 0.1% group, −0.90±0.66 D in 0.5% group) was similar to that in children originally assigned to the 0.01% group, who required re-treatment during phase 1 (−0.77±0.49 D, $P > 0.286$), suggesting that re-treatment with 0.01% was as effective as primary treatment with atropine 0.01% (Table 3).

Overall, fewer eyes progressed by ≥2.0 D in the original atropine 0.01% (27%) group compared with those in the 0.1% (41%) and 0.5% (47%) groups at the end of the study ($P = 0.006$) (Fig 4). The percentages of high myopia (myopia ≥6.0 D) in both eyes was 44%, 49%, and 50% in the atropine 0.01%, 0.1%, and 0.5% groups, respectively ($P = 0.70$). Very high myopia (myopia of ≥8.0 D in both eyes) was noted in 7%, 9%, and 17% of children in the 0.01%, 0.1%, and 0.5% groups, respectively ($P = 0.07$).

Change in Axial Length

There was no significant difference in AL in all 3 atropine groups at the start of phase 3 ($P = 0.653$) (Fig 5). However, by the end of phase 3, the mean change in AL was smaller in the 0.01% group (0.19±0.18 mm) compared with the 0.1% (0.24±0.21 mm, $P = 0.042$) and 0.5% (0.26±0.23 mm, $P = 0.013$) groups (Table 3). The mean overall change in AL over 5 years was 0.75±0.48

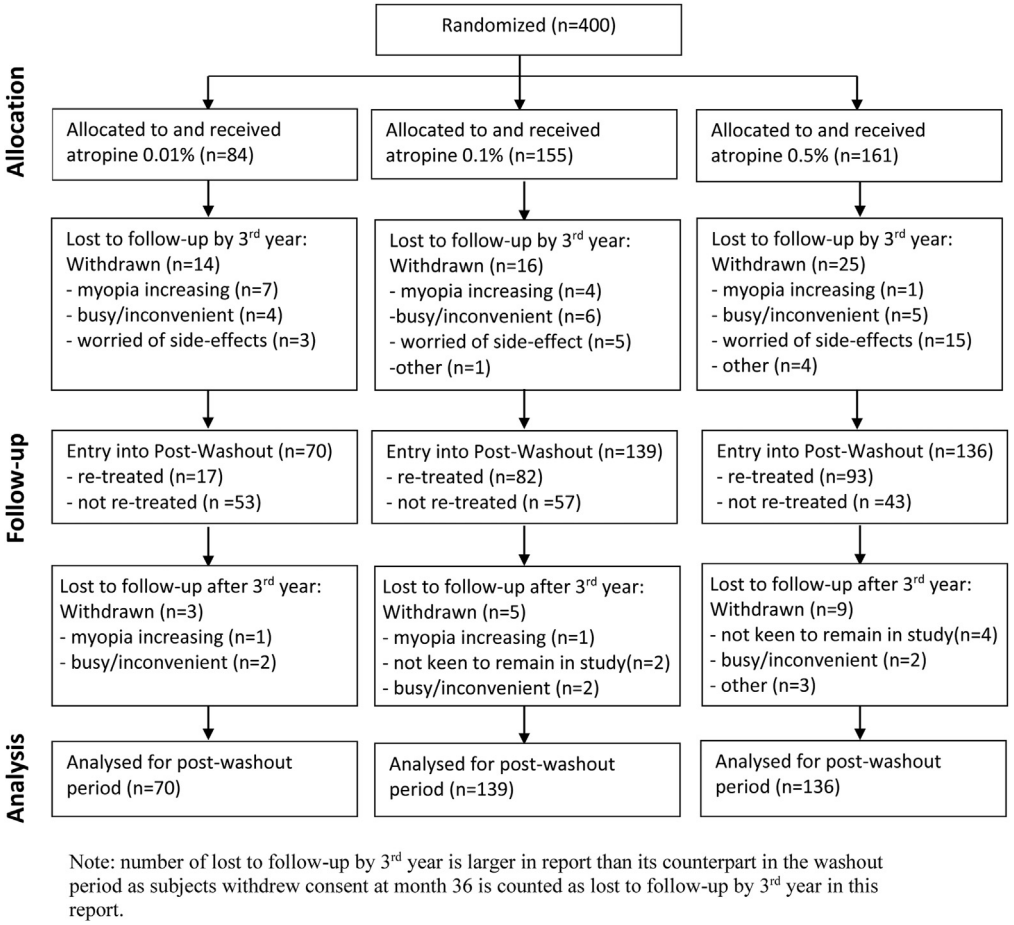


Figure 1. Subject flowchart of Atropine for the Treatment of Myopia (ATOM) 2.

mm, 0.85±0.53 mm, and 0.87±0.49 mm in the 0.01%, 0.1%, and 0.5% groups, respectively ($P = 0.185$).

In the children who were not restarted on atropine, AL elongation gradually slowed during phase 3 and there was no difference in AL among groups at 5 years ($P = 0.555$) (Table 3). In children in whom atropine was restarted, AL elongation slowed in all groups (0.32±0.22 mm in 0.01% group, 0.27±0.25 mm in 0.1% group, 0.29±0.25 mm in 0.5% group) over phase 3 to a rate lower than that noted during phase 1 in the 0.01% group that required re-treatment (0.58±0.27 mm, $P < 0.001$).

Change in Pupil Size, Accommodation, and Distance/Near Vision

At 36 months, before restarting children on atropine, the pupil size, accommodation, and near vision were similar in all 3 groups

Table 1. Comparison of Subjects Who Required Re-treatment and Those Who Did Not, and Those Still in Study and Those Lost To Follow-up at 3 Years

	Re-treated Children n = 192 (55.6%)	Untreated Children n = 153 (44.4%)	*P* Value	Still in Study (at 3 Years) n = 345 (86.2%)	Lost to Follow-up n = 55 (13.8%)	*P* Value
Age at screening, yrs, mean (SD)	9.1 (1.3)	10.5 (1.2)	<0.001	9.7 (1.5)	9.5 (1.9)	0.329
Male, n (%)	104 (54.2)	75 (49.0)	0.386	179 (51.9)	32 (58.2)	0.467
Spherical equivalent (D)						
Baseline, mean (SD)	−4.34 (1.64)	−4.70 (1.51)	0.031	−4.50 (1.59)	−3.89 (1.71)	0.018
Change at 1 yr	−0.30 (0.47)	−0.20 (0.48)	0.033	−0.25 (0.48)	−0.64 (0.66)	0.003
AL (mm)						
Baseline, mean (SD)	25.05 (0.91)	25.30 (0.86)	0.008	25.16 (0.90)	25.00 (0.92)	0.225
Change at 1 yr	0.17 (0.17)	0.10 (0.16)	<0.001	0.14 (0.17)	0.28 (0.29)	0.008

AL = axial length; SD = standard deviation.

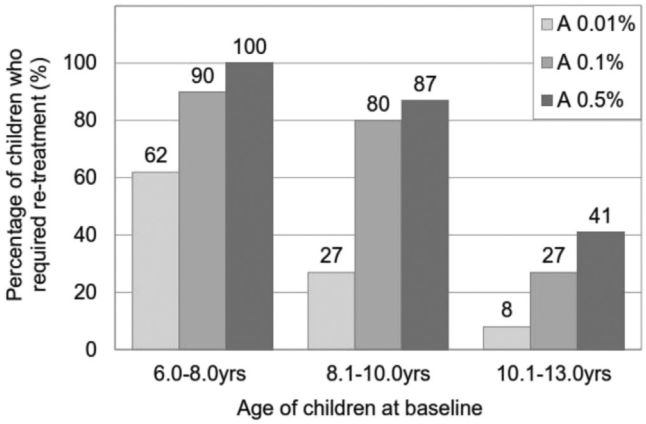


Figure 2. Percentage of children in each atropine group who required re-treatment at 3 years with atropine 0.01%, 0.1%, and 0.5% because they had progressed by more than 0.50 diopters (D) during the washout period (phase 2).

(Table 4). On restarting atropine 0.01%, there was a mean increase in photopic pupil size of approximately 1 mm and a loss of accommodation of 2.00 to 3.00 D, which were similar to the change noted in eyes treated with atropine 0.01% during phase 1 (Table 4). These mild side effects were deemed clinically insignificant, because there was no change or loss in distance or near visual acuity. Children were offered progressive addition or photochromatic (tinted) glasses if they encountered near blur or glare. During phase 1, 7% of children receiving atropine 0.01% requested glasses,[19] but no child who was restarted on atropine 0.01% requested glasses during phase 3. Pupil size and accommodation returned to levels similar to those in untreated children at the final visit (2 months after stopping atropine).

Discussion

In our first randomized placebo-controlled clinical trial using atropine eyedrops to control myopia progression in children (ATOM1), we established the clinical safety and efficacy of atropine 1% at least in the short term.[16,18] In phase 1 of ATOM2, we established that atropine 0.01% was almost as effective in reducing myopia progression as higher concentrations but with minimal pupil dilation accommodation and near vision loss.[19,20] In phase 2, we further established that children receiving lower doses had less myopic progression after atropine was stopped,[20] resulting in 0.01% being more effective in reducing myopia progression at 3 years.

In the last phase of ATOM2 (phase 3), all children with myopia progression of −0.50 D or more in the washout year were restarted on atropine 0.01% for a further 24 months. Fewer children in the 0.01% group (24%) needed re-treatment compared with children in the 0.1% (59%) and 0.5% (68%) groups (Fig 2). By the end of the study, the overall 5-year progression of myopia was less in the 0.01% group (−1.38±0.98 D) compared with the 0.1% (−1.83±1.16, $P = 0.003$) and 0.5% (−1.98±1.10 D, $P < 0.001$) groups (Fig 3). This was largely because fewer children in the 0.01% group progressed after atropine was stopped, and the rate of progression in the washout year in those who needed re-treatment was also less in the 0.01% group (−0.63 D, −0.94 D, and −1.09 D in the 0.01%, 0.1%, and 0.5% groups, respectively) (Table 3). The subsequent myopic progression in children who required re-treatment was similar between groups over the last 2 years (−0.86 to −0.91 D), which was also similar to that in children in the 0.01% group who required re-treatment over the first 2 years (−0.79 D). This suggests that re-treatment with atropine 0.01% could be as effective as primary treatment with atropine 0.01%, and that clinicians may be able to titrate treatment by stopping and restarting treatment according to individual progression rates (Table 3).

Findings from the ATOM1 and ATOM2 studies are summarized in Figure 6. Conducted a few years apart, both studies had similar study designs, with the main differences being that children in the ATOM2 study were slightly older (9.7 vs. 9.2 years) and had slightly higher levels of baseline myopia (−4.7 D vs. −3.5 D).[16,19,20] By combining the 2 studies, we found that in the initial 8 months, there was a hyperopic shift in the 1.0% group and continued myopic progression in the other groups, which was greater in the lower doses, before growth slowed between the 8- and 24-month periods. By the end of phase 1, there was clustering of mean myopia progression between 0.2 and 0.5 D in the atropine-treated eyes, compared with 1.2 D in the placebo eyes.[16,19] This plateauing of myopia progression in the second year suggests that there may be a maximal effect

Table 2. Regression Analysis of Myopic Rebound (Change in Spherical Equivalent) during Phase 2 (Washout) Period

	Unadjusted Analysis		Adjusted Analysis	
Baseline Characteristics	*Coefficient (95% CI)*	P *Value*	*Coefficient (95% CI)*	P *Value*
Age	0.16 (0.13–0.19)	<0.001	0.16 (0.13–0.18)	<0.001
Gender				
Female	0.03 (−0.07 to 0.14)	0.529	0.02 (−0.06 to 0.10)	0.584
Male	0	-	0	-
Spherical equivalent	−0.03 (−0.06 to −0.003)	0.031	−0.01 (−0.04 to 0.01)	0.229
Treatment group				
Atropine 0.01%	0	-	0	-
Atropine 0.1%	−0.40 (−0.50 to −0.31)	<0.001	−0.40 (−0.49 to −0.31)	<0.001
Atropine 0.5%	−0.60 (−0.70 to −0.49)	<0.001	−0.60 (−0.70 to −0.51)	<0.001

CI = confidence interval.

Table 3. Demographics and Changes in Spherical Equivalent and Axial Length in Children within Different Atropine Groups (0.01%, 0.1%, and 0.5%) Who Were Re-treated and Who Did Not Require Re-treatment

	Re-treated Children				Untreated Children			
	Atropine 0.01% N = 17 (24.3%)	*Atropine 0.1% N = 82 (58.9%)*	*Atropine 0.5% N = 93 (68.4%)*	***P* Value**	*Atropine 0.01% N = 53 (73.5%)*	*Atropine 0.1% N = 57 (41.1%)*	*Atropine 0.5% N = 43 (31.6%)*	***P* Value**
Age at screening, yrs, mean (SD)	8.6 (1.1)	9.0 (1.3)	9.2 (1.4)	0.261	10.0 (1.3)	10.7 (1.2)	10.9 (1.0)	<0.001
Male, n (%)	9 (52.9)	43 (52.4)	52 (55.9)	0.908	27 (50.9)	31 (54.4)	17 (39.5)	0.317
SE, D, mean (SD)								
Baseline	−4.07 (1.26)	−4.31 (1.40)	−4.41 (1.89)	0.617	−4.80 (1.55)	−4.76 (1.35)	−4.49 (1.65)	0.593
24 mos	−4.84 (1.22)	−4.84 (1.29)	−4.74 (1.76)	0.898	−5.12 (1.63)	−4.88 (1.30)	−4.63 (1.61)	0.332
36 mos	−5.47 (1.27)	−5.78 (1.28)	−5.83 (1.78)	0.554	−5.27 (1.64)	−5.18 (1.36)	−5.05 (1.54)	0.772
48 mos	−5.76 (1.42)	−6.16 (1.48)	−6.28 (1.93)	0.406	−5.58 (1.81)	−5.54 (1.51)	−5.46 (1.75)	0.939
60 mos	−6.20 (1.59)	−6.63 (1.67)	−6.77 (2.19)	0.428	−5.86 (1.85)	−5.91 (1.75)	−5.80 (1.83)	0.948
Change in SE, D, mean (SD)								
Baseline to 12 mos	−0.54 (0.43)	−0.41 (0.47)	−0.16 (0.45)	<0.001	−0.31 (0.45)	−0.14 (0.51)	−0.13 (0.44)	0.055
12−24 mos	−0.24 (0.36)	−0.12 (0.41)	−0.17 (0.40)	0.419	−0.01 (0.36)	0.02 (0.37)	−0.05 (0.37)	0.638
24−36 mos	−0.63 (0.31)	−0.94 (0.33)	−1.09 (0.43)	<0.001	−0.16 (0.24)	−0.30 (0.30)	−0.38 (0.34)	<0.001
36−48 mos	−0.42 (0.47)	−0.38 (0.50)	−0.42 (0.51)	0.880	−0.30 (0.39)	−0.36 (0.42)	−0.38 (0.37)	0.575
48−60 mos	−0.44 (0.48)	−0.52 (0.44)	−0.49 (0.56)	0.762	−0.34 (0.38)	−0.36 (0.42)	−0.32 (0.34)	0.910
Baseline to 60 mos	−2.25 (1.11)	−2.34 (1.07)	−2.32 (1.04)	0.950	−1.12 (0.77)	−1.13 (0.88)	−1.27 (0.86)	0.631
AL, mm, mean (SD)								
Baseline	24.97 (0.84)	24.97 (0.81)	25.14 (0.99)	0.419	25.37 (0.98)	25.32 (0.78)	25.21 (0.81)	0.654
24 mos	25.55 (0.89)	25.33 (0.83)	25.45 (1.05)	0.506	25.68 (1.06)	25.47 (0.81)	25.38 (0.84)	0.274
36 mos	25.89 (0.92)	25.76 (0.85)	25.87 (1.06)	0.659	25.82 (1.10)	25.66 (0.85)	25.56 (0.85)	0.385
48 mos	26.01 (0.94)	25.92 (0.91)	26.08 (1.10)	0.581	25.91 (1.10)	25.79 (0.87)	25.66 (0.86)	0.442
60 mos	26.16 (0.98)	26.07 (0.95)	26.20 (1.14)	0.692	25.96 (1.11)	25.86 (0.88)	25.74 (0.88)	0.555
Change in AL, mm, mean (SD)								
Baseline to 12 mos	0.30 (0.15)	0.18 (0.17)	0.13 (0.16)	<0.001	0.18 (0.15)	0.05 (0.16)	0.06 (0.15)	<0.001
12−24 mos	0.28 (0.15)	0.19 (0.13)	0.18 (0.11)	0.020	0.14 (0.13)	0.10 (0.11)	0.11 (0.10)	0.183
24−36 mos	0.34 (0.13)	0.43 (0.14)	0.42 (0.18)	0.007	0.14 (0.09)	0.18 (0.12)	0.17 (0.14)	0.093
36−48 mos	0.17 (0.15)	0.15 (0.15)	0.17 (0.16)	0.742	0.08 (0.09)	0.13 (0.10)	0.10 (0.09)	0.018
48−60 mos	0.15 (0.11)	0.12 (0.12)	0.12 (0.13)	0.572	0.06 (0.08)	0.07 (0.09)	0.08 (0.10)	0.550
Baseline to 60 mos	1.21 (0.54)	1.08 (0.53)	1.03 (0.47)	0.372	0.60 (0.35)	0.54 (0.34)	0.54 (0.34)	0.495

AL = axial length; D = diopter; SD = standard deviation; SE = spherical equivalent.

after which higher doses are ineffective. After stopping atropine, there was a significant myopic progression in eyes receiving higher doses with myopia than in eyes previously receiving atropine 1.0%, almost approaching that of placebo eyes, with less change noted in lower doses.[18,20]

Much of the changes noted could be explained by the pharmacologic effect of atropine on the actively growing myopic eye. Although the exact mechanism of atropine is not known, it is believed that atropine acts directly or indirectly on the retina or scleral, inhibiting thinning or stretching of the scleral, and thereby eye growth.[20,22] This eye growth possibly involves a series of biochemical steps, and atropine presumably inhibits 1 or more steps along this pathway, creating changes in the feedback mechanisms and up- or downregulating other receptors both up- and downstream. When atropine is withdrawn, it is not surprising that there may be a sudden growth spurt as the inhibitory action is released. If the process involved a simple inhibition of growth, then one would expect that after a sudden increase, eyeball growth would then slow to a rate appropriate for age. However, the rate of growth seemed to continue at a steady pace over the washout year in children previously receiving the higher 0.1% and 0.5% doses of atropine, slowing only when atropine 0.01% was restarted. This suggests that the effects, particularly of higher doses of atropine, may be more complex than we think, possibly causing change or modification of the mechanism regulating eye growth at different anatomic and biochemical levels.[20,22] It is uncertain whether these changes could be permanent (e.g., resulting in sustained acceleration of myopia even years after stopping atropine), the system will reset itself, or we can modulate subsequent eye growth (e.g., by tapering atropine more slowly over time). Somewhat reassuring is the finding that the proportion of children who progressed >0.5 D in the washout year (i.e., requiring re-treatment) decreased with increasing age in all 3 treatment arms (Fig 2). From clinical experience, we also note that by slowly tapering the frequency of atropine, we can dampen the change in myopia and retain the beneficial effect on myopia progression. In contrast, the change in myopia progression after stopping atropine 0.01% seemed less marked, and it is hoped as AL growth slowed naturally, as it did during phase 3, that atropine could be safely stopped (e.g., by the mid to late-teens).

On the basis of these results, we conclude that low-dose (0.01%) atropine for periods up to 5 years is a clinical viable

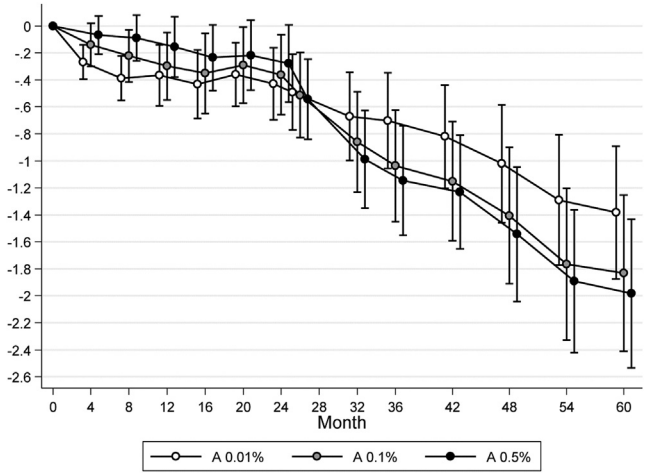


Figure 3. Mean change in spherical equivalent over time within different treatment groups (atropine 0.01%, 0.1%, and 0.5%). Error bars represent 1 standard deviation.

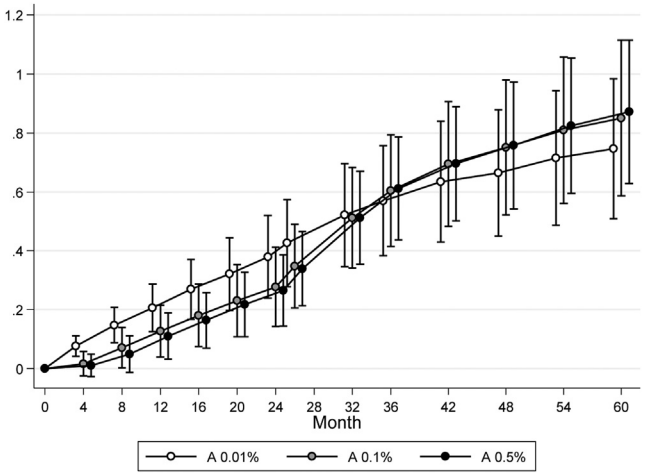


Figure 5. Mean change in axial length (AL) over time within different treatment groups (atropine 0.01%, 0.1%, and 0.5%). Error bars represent 1 standard deviation.

treatment of myopia with the best sustained effect on myopia retardation. The mean myopia progression at 5 years (−1.38 D) in children initially randomized to atropine 0.01% was similar to that in placebo eyes at 2.5 years (−1.40 D), suggesting that atropine 0.01% slowed myopia progression by 50% (Fig 6).[18] The gradual slowing of the myopia progression and corresponding AL change in the later years in phase 3 (i.e., 54−60 months) in the 0.01% group suggested that eye growth was slowing and that a long-term sustained effect was possible, as suggested in several other studies.[4,8,23]

In establishing clinical treatment algorithms, however, questions remain on which children would best benefit from treatment (e.g., in terms of age, level of myopia, rate of progression, and family risk factors), when atropine should be started and stopped, and for how long it should be used. In our studies, children underwent a washout period of a full 1 year after 2 years of treatment, which clinically would not be necessary, and it is possible that if atropine had been continued longer, particularly in children whose myopia increased after atropine was stopped, then the overall effect may have been even better. Although one may speculate as to the safety and efficacy profiles of other low doses (e.g., 0.005% or 0.05%), the 0.01% dose appears to offer an appropriate risk−benefit ratio, with no clinically significant visual side effects balanced against a reasonable and clinically significant 50% reduction in myopia progression. This is corroborated by cohort studies that show that doses of 0.025% to 0.05% could be very effective.[23] Further studies could explore if there is still a role for high-dose atropine (e.g., for rapid progressors) and the additive effect of combining atropine with other emerging myopia therapies (e.g., peripheral defocus contact lenses or spectacles) and environmental interventions (e.g., increased outdoor time).[24]

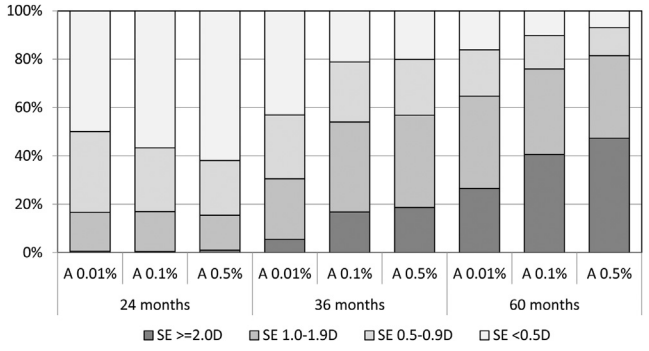


Figure 4. Myopic progression in eyes within each atropine group at the end of phase 1 (24 months), phase 2 (36 months), and phase 3 (60 months). D = diopter; SE = spherical equivalent.

Within the confines of our finding, we propose that a daily dose of atropine 0.01% is an effective first-line treatment in children aged 6 to 12 years with documented myopic progression of ≥0.5 D in the preceding year with few side effects. Because atropine appeared more effective in the second year than the first, treatment initially should be continued for at least 2 years. If there is a good response to atropine 0.01% (e.g., almost no progression or progression <0.25 D in the second year) especially in older children aged >13 years, then atropine 0.01% could be stopped. If an increase in myopia then occurs, then children could be restarted on atropine. If the initial response to atropine was more moderate (e.g., progression of 0.25−0.75 D in the second year), then one could consider continuing atropine 0.01% for a longer period until progression slows to <0.25 D per year, as it might do in the mid to late teens.

However, there may be children who are poor responders to atropine. In phase 1, 9.3% of children in the 0.01% group, 6.4% of children in the 0.1% group, and 4.3% of children in the 0.5% group had myopia progression ≥1.5 D over the first 2 years of treatment. In children who respond poorly to atropine 0.01% (e.g., progress >0.75 D per year in the second year), it may be possible that they would also not respond to higher doses and that atropine should be stopped.

Table 4. Changes in Pupil Size, Accommodation, and Visual Acuity in Children within Different Atropine Groups (0.01%, 0.1%, and 0.5%) Who Were Re-treated and Who Did Not Require Re-treatment

	Re-treated Children				Untreated Children			
	Atropine 0.01% (N = 17)	*Atropine 0.1% (N = 82)*	*Atropine 0.5% (N = 93)*	***P* Value**	*Atropine 0.01% (N = 53)*	*Atropine 0.1% (N = 57)*	*Atropine 0.5% (N = 43)*	***P* Value**
Photopic pupil size, mm, mean (SD)								
Screening	3.93 (0.56)	4.01 (0.62)	3.98 (0.63)	0.872	3.89 (0.58)	3.86 (0.67)	4.02 (0.60)	0.363
24 mos	5.18 (1.02)	6.76 (1.04)	7.65 (1.06)	<0.001	5.02 (0.92)	6.46 (1.07)	7.28 (1.46)	<0.001
36 mos	3.78 (0.58)	3.76 (0.57)	3.76 (0.63)	0.993	3.73 (0.58)	3.59 (0.49)	3.74 (0.47)	0.193
48 mos	4.89 (0.99)	4.78 (0.87)	4.86 (0.95)	0.775	3.63 (0.52)	3.59 (0.51)	3.68 (0.40)	0.633
60 mos	5.13 (0.89)	4.79 (0.90)	4.77 (0.98)	0.275	3.58 (0.59)	3.48 (0.49)	3.58 (0.46)	0.448
Final visit	3.81 (0.59)	3.59 (0.54)	3.56 (0.51)	0.264	3.58 (0.59)	3.48 (0.49)	3.58 (0.46)	0.448
Accommodation, D, mean (SD)								
Screening	17.29 (3.24)	17.13 (3.12)	15.95 (3.68)	0.041	15.99 (3.15)	16.83 (2.72)	15.93 (2.76)	0.149
24 mos	10.88 (4.01)	6.18 (2.76)	3.89 (2.33)	<0.001	11.95 (2.73)	7.53 (3.58)	4.55 (3.16)	<0.001
36 mos	13.55 (2.49)	14.58 (2.79)	13.30 (2.96)	0.010	14.18 (3.04)	14.26 (2.29)	13.07 (2.17)	0.015
48 mos	11.37 (3.21)	11.66 (2.62)	11.17 (3.11)	0.530	13.61 (2.60)	13.42 (2.81)	12.34 (2.10)	0.013
60 mos	11.01 (3.20)	10.92 (2.45)	10.57 (2.83)	0.638	12.98 (2.58)	12.56 (2.48)	12.29 (2.13)	0.348
Final visit	13.44 (2.48)	12.93 (2.28)	12.26 (2.87)	0.107	12.98 (2.58)	12.56 (2.48)	12.29 (2.13)	0.348
Distance visual acuity, logMAR, mean (SD)								
Screening	0.02 (0.03)	0.02 (0.07)	0.03 (0.06)	0.527	0.01 (0.05)	−0.00 (0.06)	0.00 (0.05)	0.333
24 mos	0.01 (0.05)	0.01 (0.05)	0.02 (0.06)	0.539	−0.01 (0.06)	−0.01 (0.06)	−0.01 (0.05)	0.992
36 mos	−0.01 (0.05)	0.00 (0.05)	0.00 (0.05)	0.700	−0.01 (0.05)	−0.02 (0.05)	−0.01 (0.05)	0.843
48 mos	−0.00 (0.04)	0.00 (0.05)	0.00 (0.05)	0.822	−0.02 (0.05)	−0.02 (0.06)	−0.01 (0.04)	0.867
60 mos	−0.01 (0.05)	−0.01 (0.05)	0.00 (0.05)	0.120	−0.02 (0.05)	−0.02 (0.06)	−0.03 (0.05)	0.286
Final visit	−0.02 (0.04)	−0.02 (0.05)	−0.01 (0.05)	0.444	−0.02 (0.05)	−0.02 (0.06)	−0.03 (0.05)	0.286
Near visual acuity, logMAR, mean (SD)								
Screening	0.04 (0.08)	0.07 (0.08)	0.04 (0.07)	0.059	0.03 (0.06)	0.02 (0.07)	0.02 (0.06)	0.440
24 mos	0.03 (0.07)	0.13 (0.13)	0.30 (0.16)	<0.001	0.01 (0.07)	0.07 (0.12)	0.27 (0.22)	<0.001
36 mos	0.00 (0.05)	−0.01 (0.06)	−0.00 (0.06)	0.434	−0.02 (0.05)	−0.02 (0.06)	−0.02 (0.06)	0.676
48 mos	−0.01 (0.06)	0.01 (0.05)	0.01 (0.07)	0.728	−0.01 (0.05)	−0.02 (0.06)	−0.03 (0.06)	0.049
60 mos	0.01 (0.06)	−0.01 (0.06)	−0.00 (0.07)	0.535	−0.02 (0.05)	−0.02 (0.06)	−0.04 (0.05)	0.191
Final visit	−0.00 (0.05)	−0.02 (0.06)	−0.01 (0.06)	0.451	−0.02 (0.05)	−0.02 (0.06)	−0.04 (0.05)	0.191

D = diopters; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation.

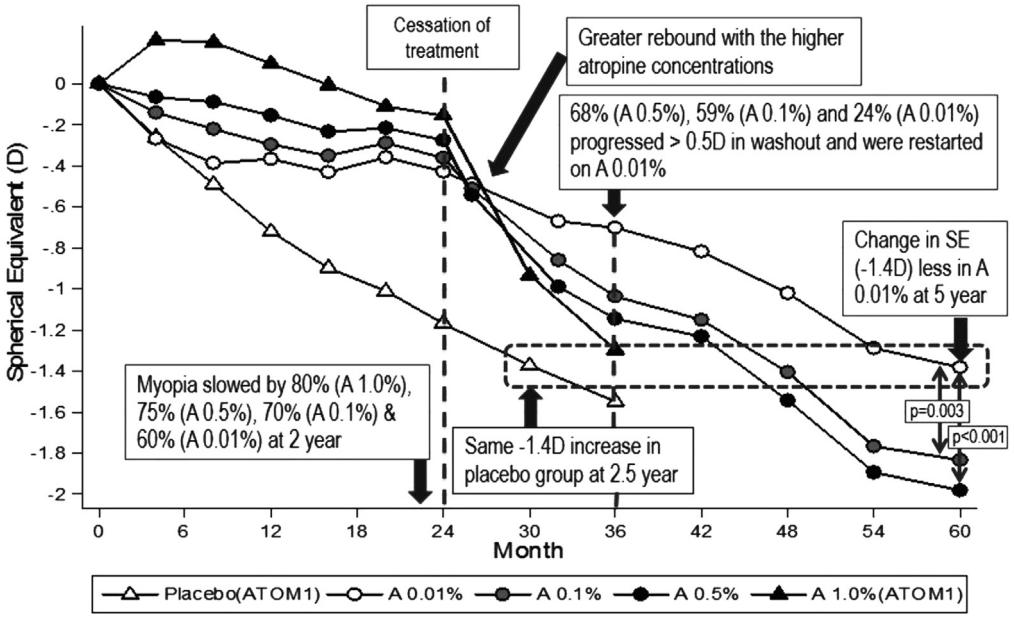


Figure 6. Summary of findings from the ATOM1 and ATOM2 studies: change in spherical equivalent (SE). ATOM = Atropine for the Treatment of Myopia; D = diopter.

An ultimate goal of myopia control therapy would be to slow myopic progression during the years of most active eye growth so that the eventual level of myopia was lower than if the eye was allowed to grow naturally (i.e., to reduce the incidence of high myopia). If less people developed high or pathologic myopia, then less might also develop the potentially blinding myopic complications, such as posterior staphyloma, macula choroidal neovascularization, retinal detachment, and glaucoma.[25–27] In a recent review, pathologic myopia was estimated to have a global prevalence of 0.9% to 3.1% and to be the cause of low vision or blindness in 5.8% to 7.8% in European populations and 12.2% to 31.3% in East Asian populations.[26] Given the increasing prevalence of myopia in East Asia, where the prevalence of myopia in young adults now approaches 80% and high myopia rates exceed 20%, it is thought that the disease burden and cost of pathologic myopia will continue to increase over time.[27] The availability of an effective and low-cost myopia-retarding medication such as atropine 0.01% is timely and could make both clinical and economic sense as a public health measure. The role of higher doses of atropine remains debatable, and care should be taken in stopping it suddenly, particularly in younger children. The strength of this study is in its randomized double-blind design, its relatively low loss to follow rate, and its long duration. Unfortunately, the lack of a control group in this study severely limited our ability to evaluate the full effect of atropine, necessitating comparison with historic and population-based data. Further studies are still needed to determine how eye growth is altered in the long term in children treated with varying doses of atropine so as to better assess the true long-term efficacy and safety of this medication.

References

1. Gimbel HV. The control of myopia with atropine. Can J Ophthalmol 1973;8:527–32.
2. Kelly TS, Chatfield C, Tustin G. Clinical assessment of the arrest of myopia. Br J Ophthalmol 1975;59:529–38.
3. Bedrossian RH. The effects of atropine on myopia. Ophthalmology 1979;86:713–7.
4. Brodstein RS, Brodstein DE, Olson RJ, et al. The treatment of myopia with atropine and bifocals. A long-term prospective study. Ophthalmology 1984;91:1373–9.
5. Brenner RL. Further observations on use of atropine in the treatment of myopia. Ann Ophthalmol 1985;17:137–40.
6. Chou AC, Shih YF, Ho TC, Lin LL. The effectiveness of 0.5% atropine in controlling high myopia in children. J Ocul Pharmacol Ther 1997;13:61–7.
7. Romano PE, Donovan JP. Management of progressive school myopia with topical atropine eyedrops and photochromic bifocal spectacles. Binocul Vis Strabismus Q 2000;15:257–60.
8. Kennedy RH, Dyer JA, Kennedy MA, et al. Reducing the progression of myopia with atropine: a long term cohort study of Olmsted County students. Binocul Vis Strabismus Q 2000;15(suppl):281–304.
9. Chiang MF, Kouzis A, Pointer RW, Repka MX. Treatment of childhood myopia with atropine eyedrops and bifocal spectacles. Binocul Vis Strabismus Q 2001;16:209–15.
10. Syniuta LA, Isenberg SJ. Atropine and bifocals can slow the progression of myopia in children. Binocul Vis Strabismus Q 2001;16:203–8.
11. Lee JJ, Fang PC, Yang IH, et al. Prevention of myopia progression with 0.05% atropine solution. J Ocul Pharmacol Ther 2006;22:41–6.
12. Fan DS, Lam DS, Chan CK, et al. Topical atropine in retarding myopic progression and axial length growth in children with moderate to severe myopia: a pilot study. Jpn J Ophthalmol 2007;51:27–33.
13. Yen MY, Liu JH, Kao SC, Shiao CH. Comparison of the effect of atropine and cyclopentolate on myopia. Ann Ophthalmol 1989;21:180–2, 187.
14. Shih YF, Chen CH, Chou AC, et al. Effects of different concentrations of atropine on controlling myopia in myopic children. J Ocul Pharmacol Ther 1999;15:85–90.
15. Shih YF, Hsiao CK, Chen CJ, et al. An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression. Acta Ophthalmol Scand 2001;79:233–6.
16. Chua WH, Balakrishnan V, Chan YH, et al. Atropine for the treatment of childhood myopia. Ophthalmology 2006;113:2285–91.
17. Liang CK, Ho TY, Li TC, et al. A combined therapy using stimulating auricular acupoints enhances lower-level atropine eyedrops when used for myopia control in school-aged children evaluated by a pilot randomized controlled clinical trial. Complement Ther Med 2008;16:305–10.
18. Tong L, Huang XL, Koh AL, et al. Atropine for the treatment of childhood myopia: effect on myopia progression after cessation of atropine. Ophthalmology 2009;116:572–9.
19. Chia A, Chua WH, Cheung YB, et al. Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (ATOM2). Ophthalmology 2012;119:347–54.
20. Chia A, Chua WH, Li W, et al. Atropine for the treatment of childhood myopia: changes after stopping atropine 0.01%, 0.1% and 0.5% (ATOM2). Am J Ophthalmol 2014;157:451–7.
21. Williams RL. A note on robust variance estimation for cluster-correlated data. Biometrics 2000;56:645–6.
22. McBrien NA, Stell WK, Carr B. How does atropine exert its anti-myopia effects? Ophthalmic Physiol Opt 2013;33:373–8.
23. Wu PC, Yang YH, Fang PC. The long-term results of using low-concentration atropine eye drops for controlling myopia progression in schoolchildren. J Ocul Pharmacol Ther 2011;27:461–6.
24. Russo A, Semeraro F, Romano MR, et al. Myopia onset and progression: can it be prevented? Int Ophthalmol 2014;34:693–705.
25. Saw SM, Gazzard G, Shih-Yen EC, Chua WH. Myopia and associated pathological complications. Ophthalmic Physiol Opt 2005;25:381–91.
26. Hayashi K, Ohno-Matsui K, Shimada N, et al. Long-term pattern of progression of myopic maculopathy: a natural history study. Ophthalmology 2010;117:1595–611.
27. Wong TY, Ferreira A, Hughes R, et al. Epidemiology and disease burden of pathological myopia and myopic choroidal neovascularization: an evidence-based systemic review. Am J Ophthalmol 2014;157:9–25.

Footnotes and Financial Disclosures

Originally received: June 25, 2014.
Final revision: June 8, 2015.
Accepted: July 2, 2015.
Available online: August 11, 2015. Manuscript no. 2014-1001.

[1] Singapore National Eye Center, Singapore.
[2] Singapore Eye Research Institute, Singapore.
[3] Singapore Clinical Research Institute, Singapore.
[4] Duke NUS Graduate Medical School, Singapore.
[5] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore.

Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

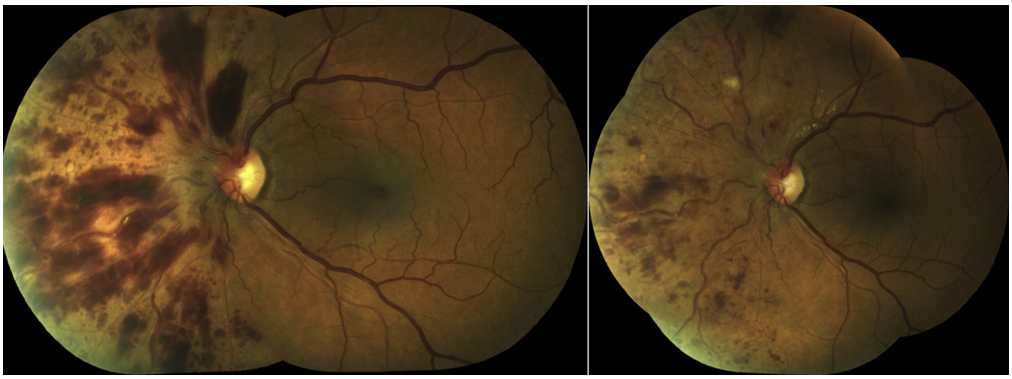
Supported by grants from the National Medical Research Council (MH 95:03/1-23) and SingHealth (SHF/FG039/2004 and TEST 08-03).

Author Contributions:
Conception and design: Chia, Lu, Tan
Data acquisition and/or research execution: Chia, Lu, Tan
Analysis and interpretation: Chia, Lu, Tan
Obtained funding: Tan
Overall responsibility: Chia, Lu, Tan

Abbreviations and Acronyms:
AL = axial length; **ATOM** = Atropine for Treatment of Myopia; **D** = diopters.

Correspondence:
Donald Tan, FRCS, FRCOphth, Singapore National Eye Center, 11 Third Hospital Ave., Singapore 168751. E-mail: donald.tan.t.h@snec.com.sg.

Pictures & Perspectives



Nasal Hemiretinal Vein Occlusion

It is axiomatic that the retinal vasculature bifurcates into superior and inferior hemispheric distributions. Hemi-retinal vein occlusions (RVO) invariably present as superior or inferior retinal disease. However, we present an unusual patient with a purely nasal hemi-RVO.

A 59-year-old hypertensive woman presented with a complaint of temporal photopsias in the left eye. The left eye was found to have a marked venous dilatation and diffuse retinal hemorrhages throughout the nasal retinal hemisphere. The hemi-RVO resolved without evolving into a typical central retinal vein occlusion. This patient demonstrates anomalous vascular development of the retina, in which the venous distribution corresponds to temporal and nasal retinal hemispheres.

Edward Chaum, MD, PhD
Stephen Huddleston, MD
Joseph Mastellone

University of Tennessee Health Science Center, Hamilton Eye Institute, Memphis, Tennessee