

Effect of Dual-Focus Soft Contact Lens Wear on Axial Myopia Progression in Children

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Purpose: To test the efficacy of an experimental Dual-Focus (DF) soft contact lens in reducing myopia progression.

Design: Prospective, randomized, paired-eye control, investigator-masked trial with cross-over.

Participants: Forty children, 11–14 years old, with mean spherical equivalent refraction (SER) of -2.71 ± 1.10 diopters (D).

Methods: Dual-Focus lenses had a central zone that corrected refractive error and concentric treatment zones that created 2.00 D of simultaneous myopic retinal defocus during distance and near viewing. Control was a single vision distance (SVD) lens with the same parameters but without treatment zones. Children wore a DF lens in 1 randomly assigned eye and an SVD lens in the fellow eye for 10 months (period 1). Lens assignment was then swapped between eyes, and lenses were worn for a further 10 months (period 2).

Main Outcome Measures: Primary outcome was change in SER measured by cycloplegic autorefractometry over 10 months. Secondary outcome was a change in axial eye length (AXL) measured by partial coherence interferometry over 10 months. Accommodation wearing DF lenses was assessed using an open-field autorefractor.

Results: In period 1, the mean change in SER with DF lenses (-0.44 ± 0.33 D) was less than with SVD lenses (-0.69 ± 0.38 D; $P < 0.001$); mean increase in AXL was also less with DF lenses (0.11 ± 0.09 mm) than with SVD lenses (0.22 ± 0.10 mm; $P < 0.001$). In 70% of the children, myopia progression was reduced by 30% or more in the eye wearing the DF lens relative to that wearing the SVD lens. Similar reductions in myopia progression and axial eye elongation were also observed with DF lens wear during period 2. Visual acuity and contrast sensitivity with DF lenses were not significantly different than with SVD lenses. Accommodation to a target at 40 cm was driven through the central distance-correction zone of the DF lens.

Conclusions: Dual-Focus lenses provided normal acuity and contrast sensitivity and allowed accommodation to near targets. Myopia progression and eye elongation were reduced significantly in eyes wearing DF lenses. The data suggest that sustained myopic defocus, even when presented to the retina simultaneously with a clear image, can act to slow myopia progression without compromising visual function.

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Myopia imposes significant burdens on society. The costs related to its optical correction are high,^{1,2} and common myopia increases the risk of associated glaucoma^{3,4} and cataract.^{5,6} High axial myopia also increases the risk of retinal detachment, chorioretinal degeneration, and subsequent visual impairment.^{7,8} The prevalence of both common and high myopia has increased significantly over recent years.^{9,10} The overall prevalence in the United States is now approximately 40%,¹¹ and in some Asian centers more than 80% of Chinese young people may be myopic.^{10,12} Although optical corrections including refractive surgery restore acuity, they do not prevent the abnormal enlargement of the myopic eye; thus, children with myopia remain at increased risk of ocular disease later in life. Attempts to slow childhood myopia progression by optical means have

had mixed results. Studies using Progressive Addition Lenses (PALs) have shown a small beneficial effect^{13–15} or no effect,^{16,17} whereas binocular under-correction may slightly accelerate progression.¹⁸ In comparison, pharmacologic interventions with antimuscarinic eye drops, such as pirenzepine^{19,20} and particularly atropine,^{21–23} seem more successful in slowing progression. However, in practice, atropine or pirenzepine would need to be administered for several years, and the long-term toxicity of antimuscarinic agents on ocular tissues is uncertain. Thus, there are currently no methods that are widely accepted as safe and effective for long-term general use in slowing myopia progression.

In developing animal eyes, myopic retinal defocus (in which the plane of focus is located in front of the retina)

created by plus-powered lens wear causes reduced axial eye growth and the development of hyperopia.^{24–26} Recent animal studies investigating the relative importance of central versus peripheral defocus have shown that peripheral defocus can have a powerful influence on refractive development in infant monkeys.^{27,28} However, human studies are equivocal about the contribution of peripheral defocus to the development of myopia. Some studies show no difference between peripheral refraction in myopic and emmetropic subjects,²⁹ whereas others have shown significantly more hyperopic peripheral refractions in myopic compared with emmetropic subjects.³⁰ A study of the effect of monovision in children with progressing myopia showed that the under-corrected eyes, which experienced sustained myopic defocus over the entire retina during both distance and near viewing, had less myopia progression and axial growth than contralateral eyes that were fully corrected.³¹ This reduction in progression may have resulted from the presence of myopic retinal defocus both during distance and near viewing, which differs from simple bilateral uncorrected or under-corrected myopia in which myopic defocus is only present during distance viewing.³¹ However, eyes with defocused retinal images have poor acuity.

This article reports the results of an early phase trial to test whether a Dual-Focus (DF) contact lens, designed to present a clear retinal image while simultaneously presenting 2.00 diopters (D) of sustained myopic retinal defocus during distance and near viewing, would act to slow myopia progression in children.

Materials and Methods

Study Design

The Dual-focus Inhibition of Myopia Evaluation in New Zealand (DIMENZ) study was a prospective, randomized, paired-eye comparison, investigator-masked, 20-month clinical trial with cross-over, conducted with 40 children. The experimental DF soft contact lens was worn in 1 eye while a single vision distance (SVD) soft contact lens was worn in the contralateral eye as the control. Myopia reportedly progresses at the same rate with standard soft contact lenses as with spectacles.³² The aim of this paired-eye design was to measure the efficacy of the DF lens in slowing myopia progression by comparing progression in the 2 eyes of each subject. However, if the DF lens were effective in slowing progression, anisometropia would develop over time with this design. To avoid the potential for any significant anisometropia remaining at the end of the trial, the lens allocation was crossed-over between eyes at the end of the first 10-month period (period 1) and lenses were worn for a further 10 months (period 2). This paired-eye design with cross-over allowed 2 types of analysis to be conducted: (1) a within-subject, between-eye comparison using data from periods 1 and 2 separately and (2) a more conventional cross-over analysis (a within-subject, within-eye comparison) comparing myopia progression between periods 1 and 2. Both types of analysis have the advantage of using within-subject comparisons.

Myopia progression is characterized by a change in refractive error (in the more minus direction) over time, which results from abnormal elongation of the eye. Thus, the primary outcome measure of this study was change in spherical equivalent refraction (SER) measured by cycloplegic autorefractometry over 10 months.

The secondary outcome measure was change in axial eye length (AXL) measured by partial coherence interferometry over 10 months. The secondary outcome was included to corroborate any changes in SER. The DIMENZ study adhered to the tenets of the Declaration of Helsinki, was approved by the New Zealand Health Research Council Regional Ethics Committee, and was prospectively registered with the Australian New Zealand Clinical Trial Registry (anzctr.org.au No. 12605000633684). Informed consent was obtained from parents/guardians, and assent was obtained in writing from participating children.

Participants

Children were eligible to participate if they met the following inclusion criteria: 11–14 years old at recruitment; an SER between -1.25 and -4.50 D in the least myopic eye as determined by non-cycloplegic subjective refraction; myopia progression ≥ 0.50 D in the previous 12 months, established from previous records or estimated from the current spectacle prescription; and best-corrected spectacle visual acuity of Snellen 6/6 or better in each eye and prepared to wear contact lenses for at least 8 hours per day during the study. Children were excluded if they had astigmatism ≥ 1.25 D, anisometropia ≥ 1.00 D, strabismus at distance or near as assessed by cover test, ocular or systemic pathology likely to affect refractive development or successful contact lens wear, or a birth weight of ≤ 1250 g.³³

Children were randomized into group 1 or group 2 using a permuted block design with a block size of 4. Investigators had no access to the randomization schedule. Randomization was stratified by gender and ethnicity (East Asian and other, including New Zealand European, Indian, and Maori/Pasifika) because myopia may have a higher prevalence and progression rate in girls than in boys^{34,35} and in East Asian children than in other ethnic groups.^{36,37} In group 1, the DF lens was initially worn in the dominant eye; in group 2, the DF lens was initially worn in the nondominant eye. Eye dominance was used as a stratification factor because if visual function were to be compromised with DF lens wear, then wear-compliance may have been better when the DF lens was worn in the nondominant eye. In addition, the dominant eye may have a greater degree of myopia than the nondominant eye in participants with anisometropic myopia.³⁸ At the end of the first 10 months (period 1), the DF lens was swapped to the contralateral eye and worn for a further 10 months (period 2). In each period, the fellow eye wore an SVD lens. Short trial periods of 10 months were chosen to minimize the cost of supplying the custom-made experimental contact lenses and because clear inter-eye differences in refraction and eye length were present after 9 months in a previous study of unilateral myopic retinal defocus from our laboratory.³¹

Contact Lenses

The DF soft contact lenses comprised a central correction zone surrounded by a series of treatment and correction zones (Fig 1) that together produced 2 focal planes. The optical power of the correction zones corrected the refractive error while the treatment zones produced 2.00 D of simultaneous myopic retinal defocus. The intent was to provide good acuity but also to ensure that myopic defocus was presented to the retina during both distance and near viewing. Consequently, the central correction zone was made as large as possible to stimulate accommodation and to provide good acuity, and the zone diameters were selected so that some treatment area remained within the confines of the pupil during near viewing. Zone diameters were chosen on the basis of published data relating pupil diameter to age and light-level.³⁹ A further requirement was that the correction and treatment zones

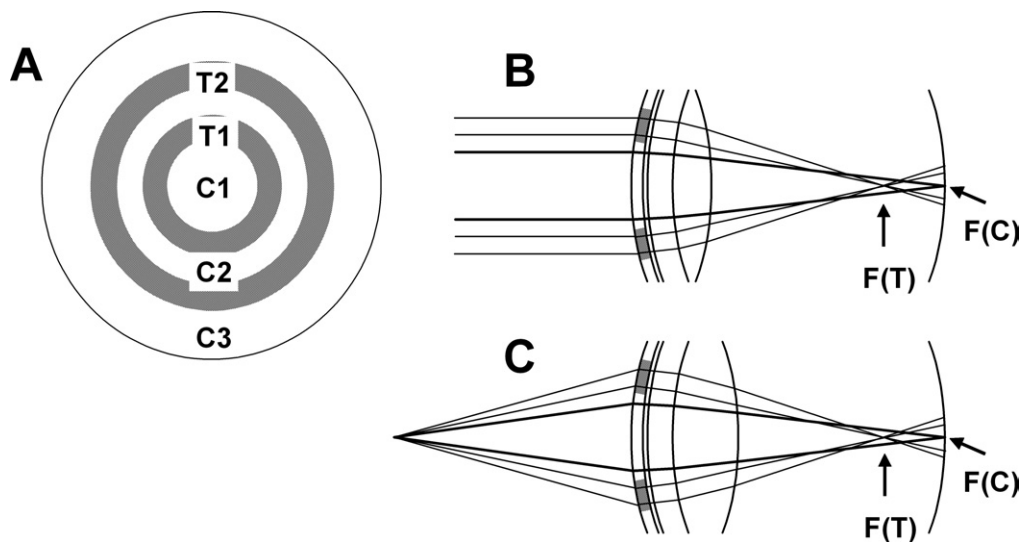


Figure 1. Design of the DF contact lens. **A**, Correction zone (outer) diameters were C1=3.36 mm, C2=6.75 mm, and C3=11.66 mm. Treatment zone (outer) diameters were T1=4.78 mm and T2=8.31 mm. **B**, During distance viewing, the focal plane F(C) of the correction zones fell on the retina and the focal plane of the treatment zones F(T) fell anterior to the retina, thus causing myopic defocus on the retina. **C**, With accommodation during near viewing, the focal plane F(C) of the correction zones was still located on (or near) the retina and the focal plane of the treatment zones F(T) remained anterior to the retina, causing myopic defocus on the retina. DF = Dual-Focus.

remained approximately equal in area as the pupil enlarged. Contact lenses were lathe cut in Hioxifilcon A (Benz Research and Development, Sarasota, FL), a non-ionic 45% water-content material with an 8.5-mm base curve and 14.2-mm total diameter. The SVD lenses were manufactured with identical parameters but without the treatment zones. Lenses were worn on a daily-wear schedule, stored overnight in disinfecting solution (Opti-free, Alcon Laboratories, Fort Worth, TX), and renewed every 2 months. Lenses and solutions were provided to the children free of charge. To avoid confusion, all right-eye lenses were blue-tinted regardless of whether they were DF or SVD lenses.

Procedures: Screening Visit

All children who responded to the invitation to participate received a comprehensive eye examination to determine whether they met the inclusion criteria for the study at a Screening Visit (Table 1, available at <http://aaojournal.org>). This assessment included measurement of visual acuity using a computerized logarithm of the minimum angle of resolution chart (Medmont AT-20R) viewed at 6 m and recorded using the visual acuity rating (VAR) scale (where VAR of 100 = Snellen 6/6). Spectacle prescription was determined by non-cycloplegic subjective refraction and recorded as the least minus lens that produced maximum visual acuity. The appropriate cylinder component of the prescription was determined by the Jackson Cross Cylinder method. The presence or absence of strabismus was determined using a standard cover test, with the patient's habitual correction in place. Heterophorias were measured at distance (6 m) and near (40 cm) on all children using the von Graefe method through the subjectively determined distance correction. Amplitude of accommodation with this distance spectacle correction was measured monocularly and then binocularly using the push-up method. Eye dominance was determined by a simple sighting test (Miles test⁴⁰) of a target at 6 m. Biomicroscopy was used to assess contact lens fit and anterior segment health, and the fundus was examined by direct ophthalmoscopy and indirect funduscopy with a 90 D lens. Children who met the inclusion criteria and agreed to participate were randomized into group 1 or 2.

Procedures: Baseline and Follow-up Visits

Contact lenses were dispensed to children at the baseline visit (Table 1, available at <http://aaojournal.org>). At this visit (and at all follow-up visits) a spherical over-refraction (no cylinder correction) was performed over the DF and SVD lenses, and monocular vision with contact lenses (recorded as VAR) was measured. Visual acuity measurements reported are the best acuity with the spherical over-refraction in place over the DF or SVD lens. During the trial, the contact lens prescription was changed if over-refraction improved visual acuity by ≥ 5 letters or if clinically indicated. At baseline and at all follow-up visits, contact lens prescription and fit were evaluated and the health of the anterior segment of the eye was examined with biomicroscopy. Pupil diameter was measured with an infrared pupillometer (Neuroptics Inc., Irvine, CA) under photopic illumination (350 lux) at distance (6 m) and at near (30 cm) and also under mesopic illumination (10 lux) at distance. Outcome measures of refraction were made by cycloplegic autorefractometry (Humphrey Autorefractor Keratometer HARK-599; Carl Zeiss Meditec AG, Jena, Germany), with 5 consecutive measures per eye. Measures were expressed in power-vector form (M , J_0 , and J_{45}),⁴¹ and the average M component was used as the SER. Outcome measures of AXL were made by partial coherence interferometry (IOLMaster, Carl Zeiss Meditec AG) and computed as the mean of 20 measures per eye. Corneal power (CP) was also measured using the IOLMaster and computed as the mean of 3 measures per eye. Measures were made 30 minutes after instilling 1 drop of 0.4% benoxinate and then 2 drops of 1% tropicamide spaced 4–6 minutes apart.⁴² The participants and the optometrist responsible for clinical care were not masked to lens assignment, but the investigating optometrists responsible for making outcome measures were masked. Contact lenses were dispensed at the baseline visit, and all children were reviewed after 2–3 weeks of contact lens wear to evaluate contact lens fit and prescription and to monitor wear time. Primary and secondary outcome measures were performed at baseline and then every 5 months for a period of 20 months. At each visit, a compliance report was completed for every child to ascertain contact lens wear time per day. Contrast sensitivity measures were performed at the 5-month visit only, in the right eye, in the left eye, and then binocularly using a Pelli-Robson chart

(Haag-Streit, Harlow, UK) viewed at 1 m distance. Results were recorded using the standard technique where the final triplet of letters in which the patient read 2 letters correctly determined the log contrast sensitivity.⁴³ Additional visits could take place if required to address any problems with contact lenses or vision, but no outcome measures were taken at these visits.

Accommodation with Contact Lenses

To ensure that myopic defocus was presented to the retina during both distance and near viewing, it was necessary to show that children accommodated to view near targets while wearing the lenses (Fig 1). If instead of accommodating, children had used the treatment zones as if they were near zones of a bifocal lens, then the correction zones would have produced hyperopic retinal defocus (focal plane located posterior to the retina) during near viewing, with the potential for exacerbating eye elongation and myopia progression. To confirm that children accommodated for near tasks when wearing the contact lenses assigned during the trial, we used an infrared open-field autorefractor (SRW-5000, Shin-Nippon, Tokyo, Japan) that allowed measurement of accommodative responses to real targets in free space under binocular viewing conditions in which disparity cues could stimulate vergence-driven accommodation. Accommodative responses were measured when children changed from viewing a distance target (at 4 m) to a near target (at 40 cm) binocularly. The distance target was the line of best acuity on a high-contrast Snellen chart; the near target was the line of best acuity on a high-contrast near letter chart positioned in front of the eye being measured. Accommodative responses were computed as the difference between autorefractor readings at distance (corrected for the 4 m viewing distance by 0.25 D) and autorefractor readings at near. Before computing differences, the SERs of the autorefractor readings were computed (as sphere + ½ cylinder). All accommodation measures were made through the single vision lens because we could not obtain reliable autorefractor readings through the DF contact lens. Accommodative responses were measured under 2 conditions: (1) children wearing their DIMENZ trial contact lens allocation (DF lens allocated to 1 eye and an SVD lens in the fellow eye); and (2) children wearing the DF lens in the same randomly allocated eye and an Single Vision Near (SVN) lens in the fellow eye (+2.50 D added to the distance prescription). In this latter condition, the near-corrected eye was focused on the near target at 40 cm and consequently would not have provided any stimulus for accommodation when viewing the near target at 40 cm. Therefore, any defocus-driven accommodative response would have been provided by the eye wearing the DF lens. This SVN condition was included to provide a conservative estimate of the accommodative response that would occur should the lenses be worn binocularly. Ten consecutive measures of accommodation were taken on each subject on 3 separate occasions (at the 2-week, 10-month, and 20-month visits). Accommodative responses were not significantly different on the 3 separate occasions (with SVD lenses, $P = 0.81$; with SVN lenses, $P = 0.31$; repeated-measures analysis of variance), so the accommodation responses reported in the “Results” section represent the average of 30 readings for each child.

Statistical Analysis

Sample size was calculated for a within-subject comparison study⁴⁴ with 90% power, $P = 0.01$, difference of means = 0.25 D, intra-subject standard deviation (SD) of 0.26 D for cycloplegic autorefractor,⁴⁵ and an estimated drop out of 15%. Regression analyses were conducted in Excel (Microsoft Corp., Redmond, WA). Mixed-models analyses were carried out using the Statistical Analysis System (SAS-V8, SAS Inc., Cary, NC) to give a more

precise estimate of treatment effects because it permitted use of all available data and flexibility in modeling time effects with no attempt at imputation or adjustment for missing values. The paired-eye with cross-over study design allowed the following analyses to be conducted.

Cross-Over Analysis. This analysis, in which the treatment effect is estimated using the differences in pairs of observations for each subject, considered the overall progression of myopia over both periods and revealed significant treatment-by-time ($P = 0.0133$) and treatment-by-period ($P = 0.0024$) interactions. The presence of these interactions suggested that the underlying rate of myopia progression was not constant across periods 1 and 2 or that there was some carry-over, rebound, or other unknown factor that affected the results in period 2. Whatever the cause, efficacy could not validly be determined⁴⁶ by comparison of outcome measures in periods 1 and 2, and the results of the cross-over analysis are not presented in the “Results” section. Rather, analysis of the between-eye data in periods 1 and 2 were conducted separately.

Paired-eye Comparison Analysis. Analyses of the between-eye data in periods 1 and 2 were conducted separately. Mixed-effects models were fitted using the PROC MIXED procedure in SAS and the restricted maximum likelihood algorithm. Analyses were based on intention-to-treat principles without imputation for missing data. Although the validity of the between-eye data from period 1 cannot have been affected by the period interactions discussed above, the data from period 2 may have been affected and so must be interpreted with reservation. Where mean data are reported in the “Results” section, the confidence intervals (CIs) are ± 1 SD unless otherwise indicated.

Results

Baseline Measures

Baseline demographic, refractive, and ocular component data are summarized in Table 2 (available at <http://aaojournal.org>). At baseline, there were no significant differences in SER, CP, or AXL between eyes wearing DF lenses in groups 1 and 2, between eyes wearing SVD lenses in groups 1 and 2, or between eyes wearing DF lenses and eyes wearing SVD lenses within either group 1 or 2. Relevant P values are given in Table 2 (available at <http://aaojournal.org>). Most children (29/40) had a small to moderate exophoria (XOP) at distance: Approximately half (21/40) had a small to moderate XOP at near. The mean heterophoria at distance was $1.4 \pm 2.1^{\Delta}$ XOP (range: 6^{Δ} XOP to 3^{Δ} esophoria [SOP]). Mean heterophoria at near was $1.3 \pm 3.4^{\Delta}$ XOP (range: 12^{Δ} XOP to 7^{Δ} SOP). Of the 40 children enrolled, 35 completed the 10-month outcome measures and 34 completed the final 20-month measures. Three children dropped out from each group. In period 1, 4 children dropped out before the 5-month outcome measures because of difficulties with handling contact lenses (1 child from group 1; 2 children from group 2) or adverse publicity regarding contact lens solutions (1 child from group 1). One child dropped out because of dislike of cycloplegia (1 child from group 2). These children were not included in the period 1 analysis. In period 2, 1 child from group 1 dropped out because of contact lens-related discomfort and was not included in the period 2 analysis.

Visual Function with Dual-Focus Lens Wear

Figure 2A (available at <http://aaojournal.org>) compares the visual acuity of eyes wearing DF lenses (from groups 1 and 2) with those wearing SVD lenses (from groups 1 and 2) for all 40 children, measured at the baseline visit. Mean acuities of eyes wearing DF lenses ($VAR = 99.9 \pm 3.5$ (range: 90–108)) and eyes wearing SVD

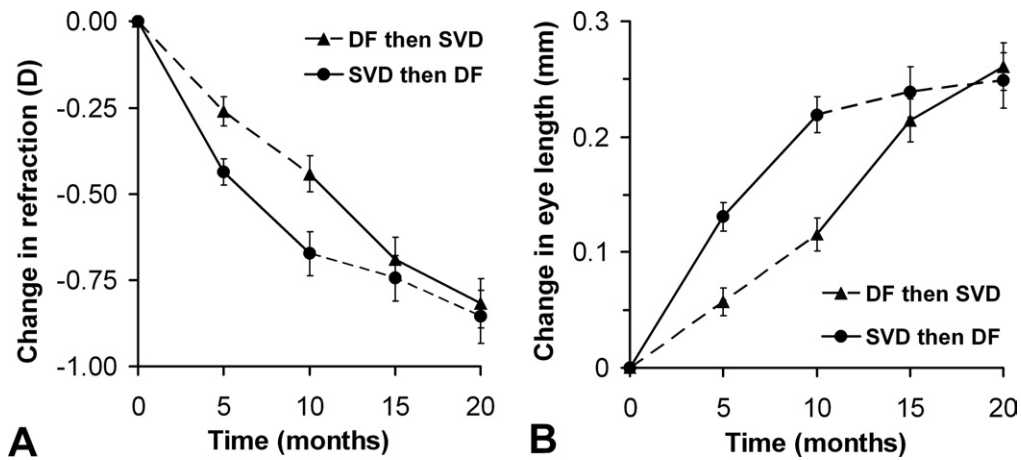


Figure 4. **A**, Mean changes (± 1 standard error of the mean) in refraction over 20 months. Filled triangles show mean change in SER in diopters in eyes that wore a DF lens in period 1 (dashed line) and an SVD lens in period 2 (solid line), i.e., filled triangles relate to the dominant eyes from participants in group 1 plus the nondominant eyes from participants in group 2. Filled circles show mean change in SER in eyes that wore an SVD lens in period 1 (solid line) and a DF lens in period 2 (dashed line), i.e., filled circles relate to the nondominant eyes from participants in group 1 plus the dominant eyes from participants in group 2. **B**, Mean changes (± 1 standard error of the mean) in eye length with time. Filled triangles show mean change in AXL (mm) in eyes that wore a DF lens in period 1 (dashed line) and an SVD lens in period 2 (solid line). Filled circles show mean change in axial length in eyes that wore an SVD lens in period 1 (solid line) and a DF lens in period 2 (dashed line). D = diopters; DF = Dual-Focus; SVD = single vision distance.

lenses (100.2 ± 2.9 , range: 95–105) were not different ($P = 0.63$). Visual acuity with contact lenses did not alter significantly throughout the trial either between eyes or within eyes. In most participants, contrast sensitivity was equal in the eyes wearing DF and SVD lenses. The mean log contrast sensitivities with DF lenses (1.56 ± 0.97) and SVD lenses (1.58 ± 0.10) were not different ($P = 0.21$). Where there was a difference between the 2 eyes, it never exceeded 1 triplet of letters on the Pelli-Robson Chart. Analysis of compliance reports showed that after 2 weeks, mean contact lens wear time was 11.90 ± 2.02 hours/day and 19 of 40 children were wearing their lenses for 7 days/week. By 20 months the mean wear time was 13.15 ± 2.80 hours/day and 27 of 34 children were wearing their lenses 7 days/week, and the remainder were wearing their lenses 6 days/week. There was no significant difference in wear time between period 1 and period 2 in group 1 ($P = 0.41$). Children in group 2 tended to have longer contact lens wearing times in period 2 (when the DF lens was worn in the dominant eye) than in period 1, although the difference did not reach statistical significance ($P = 0.07$).

Figure 2B (available at <http://aaojournal.org>) shows the accommodative responses of the children while wearing the DF lens in 1 eye and the SVN (near) lens in the other eye (DF and SVN combination), plotted versus the response when wearing the DF lens in 1 eye and the SVD lens in the other eye (DF and SVD combination). While wearing the contact lenses allocated during the trial (i.e., the DF and SVD combination), the children's mean accommodative response to a target at 40 cm was 2.07 D (95% CI, 2.62–1.52), corresponding to a mean lag of accommodation of 0.43 D relative to the distance focal plane of the DF lens. When the SVD lens was replaced by an SVN lens with an effective add of +2.50 D (the DF and SVN combination), the mean accommodative response to a target at 40 cm was reduced to 1.78 D (93% CI, 2.66–0.91; $P < 0.01$). Thus, the children did not use the DF lenses as if they were bifocal contact lenses: rather they accommodated for near viewing.

Figure 3 (available at <http://aaojournal.org>) shows the mean pupil diameters measured in eyes wearing DF lenses relative to the actual zone diameters of the DF lens, under 3 viewing conditions. With distance viewing under photopic conditions, the inner treatment zone fell within the confines of the pupil. Even with the

miosis associated with near viewing, most of the inner treatment zone still fell within the confines of the pupil. There were no significant differences in pupil size between eyes wearing DF and SVD lenses under any of the 3 conditions (photopic distance, $P = 0.75$; photopic near, $P = 0.81$; mesopic distance, $P = 0.28$).

Myopia Progression

Mean Change in Spherical Equivalent Refraction and Axial Eye Length. The progressive changes in ocular refraction and AXL over the study periods are shown graphically in Figure 4. During period 1 (baseline to 10 months), the mean increase in myopic refractive error in eyes wearing DF lenses (Table 3) was significantly less than in eyes wearing SVD lenses: Myopia progression was reduced by 37% in eyes wearing DF lenses in period 1. In addition, the mean increase in AXL was significantly less with DF lens wear than with SVD lens wear: Eye elongation was reduced by 49% in eyes wearing DF lenses in period 1. Bearing in mind the uncertainties associated with interpretation of data after cross-over (i.e., in period 2) as described in the "Materials and Methods" section, the mean increase in myopic refractive error and mean increase in eye length in eyes wearing DF lenses were also significantly less than in eyes wearing SVD lenses in period 2 (Table 3). During the 20 months of the study, mean CP increased slightly. For the 34 children completing the study, mean CP increased from 43.77 ± 1.24 D at baseline to 43.84 ± 1.20 D at 20 months ($P = 0.015$). However, the mean changes in CP in eyes wearing DF lenses and those wearing SVD lenses were not different in period 1 (DF: 0.036 ± 0.268 D; SVD: 0.029 ± 0.189 D; $P = 0.44$) or period 2 (DF: 0.057 ± 0.213 D; SVD: 0.012 ± 0.222 D; $P = 0.20$).

Group Allocation and Stratification Effects

Mixed-model analysis showed no significant interaction between group and treatment effect ($P = 0.831$), although children in group 1 had a greater rate of axial elongation in both the DF and SVD eyes than those in group 2 ($P = 0.003$). There was no difference in treatment effect of the DF lens whether it was worn in the dominant or nondominant eye in either period 1 ($P = 0.94$) or period 2 ($P = 0.71$). There was no significant difference in myopia

Table 3. Myopia Progression and Eye Elongation in Periods 1 and 2 and Percent Reductions in Progression with Dual-Focus Lens Wear

	With SVD Lens	P	With DF Lens	DF, SVD Difference	Percent Reduction
Period 1: Baseline to 10 Months					
Change in refraction (D)	-0.69±0.38	<0.0001	-0.44±0.33	0.25±0.27	37%
Eye elongation (mm)	0.218±0.089	<0.0001	0.111±0.084	0.107±0.080	49%
Period 2: Cross-over to 20 Months					
Change in refraction (D)	-0.38±0.38	0.003	-0.17±0.35	0.20±0.34	54%
Eye elongation (mm)	0.144±0.093	<0.0001	0.029±0.100	0.115±0.099	80%

DF = Dual-Focus; SVD = single vision distance.
Table entries show means ±1 SD. P values relate to differences between neighboring means.

progression (change in SER) between boys and girls in period 1 (DF eyes: $P = 0.94$; SVD eyes: $P = 0.88$) or period 2 (DF eyes: $P = 0.69$; SVD eyes: $P = 0.65$). In period 1, boys showed somewhat greater eye elongation than girls in eyes wearing SVD lenses ($P = 0.047$) but not in eyes wearing DF lenses ($P = 0.88$). In period 2, there was no significant difference in eye elongation between boys and girls in the DF eyes ($P = 0.62$) or SVD eyes ($P = 0.45$). However, greater natural growth in eye size with age has been reported in boys compared with girls.⁴⁷ Although East-Asian children showed significantly greater ($P < 0.0001$) myopia progression (both in terms of refraction and eye elongation) than others in both DF eyes (-0.54 ± 0.41 D and 0.14 ± 0.10 mm) and SVD eyes (-0.76 ± 0.52 D and 0.24 ± 0.07 mm) eyes, the treatment effects of the DF lenses were not different ($P = 0.12$) between East-Asian children (0.22 D reduction in 10 months) and other children (0.26 D reduction in 10 months). However, numbers of both boys ($n = 10$) and East Asian children ($n = 12$) in the study were limited.

Progression in Individuals

Period 1. The change in refractive error in eyes wearing SVD lenses in each trial period varied widely among children; for example, during period 1 the change in SER in eyes wearing SVD lenses ranged from -1.58 to $+0.15$ D in 10 months. To assess the efficacy of the DF lens over these widely differing progression rates, the change in refraction in the eye wearing the DF lens was plotted against the change in refraction in the fellow eye wearing the SVD lens for each individual child during period 1 (Fig 5A). Similarly, change in length of the eye wearing the DF lens was plotted against change in length of the eye wearing the SVD lens for each child in period 1 (Fig 5B). In Figure 5A and B, most data points lie below the diagonal line representing equal progression in the 2 eyes, indicating that less refractive change and eye elongation occurred in the eyes wearing the DF lenses. Although there is significant scatter in the data, the slope of the linear regression (0.55, $R = 0.68$, Fig 5A, solid line) for myopia progression in period 1 suggests that the change in refraction with DF lenses was 0.55 diopters per diopter (D/D) of progression with SVD lenses. The slope of the regression line for eye elongation in period 1 (0.54, $R = 0.57$, Fig 5B, solid line) suggests a similar proportional reduction in eye elongation (0.54 mm/mm of elongation with SVD lenses). The paired-eye nature of the refraction data also enabled the percent reduction in myopia progression with DF lens wear to be computed for each child. In period 1, 70% of children had myopia progression reduced by 30% or more; 50% had progression reduced by $\geq 50\%$; and 20% had progression reduced by $\geq 70\%$ in the eye wearing the DF lens relative to progression in the eye wearing the SVD lens.

Period 2. Regression analyses were also applied to the data from period 2. The slope of the dashed regression line for progression (0.55, $R = 0.59$, Fig 5C) and that for eye elongation (0.51, $R = 0.47$, Fig 5D) suggested a proportional reduction in progression and eye elongation with DF lenses in period 2 that was similar to that observed in period 1. However, as mentioned in the “Paired-eye Comparison Analysis” of the “Materials and Methods” section, there are some uncertainties associated with interpretation of the data in period 2 (i.e., after cross-over).

Discussion

This early-phase trial showed that eyes wearing DF contact lenses had significantly less axial myopia progression than eyes wearing SVD lenses. Dual-focus lenses also provided normal acuity and allowed accommodation to near targets. Dual-Focus lenses were designed to correct refractive error and simultaneously to retard myopia progression by providing 2.00 D of myopic retinal defocus when viewing at distance and at near. The zone diameters of the lens were designed specifically for the large pupil sizes of children. Measurements of pupil diameters in participating children showed that both correction and treatment zones fell within the pupil under both photopic and mesopic conditions and during near viewing. This suggests that during the trial, myopic retinal defocus would have been present for distance and near viewing in the eye wearing the DF lens. Thus, it would seem that sustained myopic defocus, even when presented to the retina simultaneously with a clear image, can act to slow myopia progression.

Study Design

In parallel cohort studies of myopia progression, experimental and control groups are typically matched for age and refractive error at baseline.^{13–15} However, this does not necessarily match the groups for myopia progression rate, the variable of interest, because children of the same age and with the same refractive error can be progressing at different rates.^{48,49} Our study used a paired-eye comparison design to overcome this problem. A paired-eye design matches the experimental and control eyes for myopia progression rate at baseline because an individual’s myopia normally progresses at the same rate in the 2 eyes.¹³ Such matching cannot be assumed in cohort studies unless large

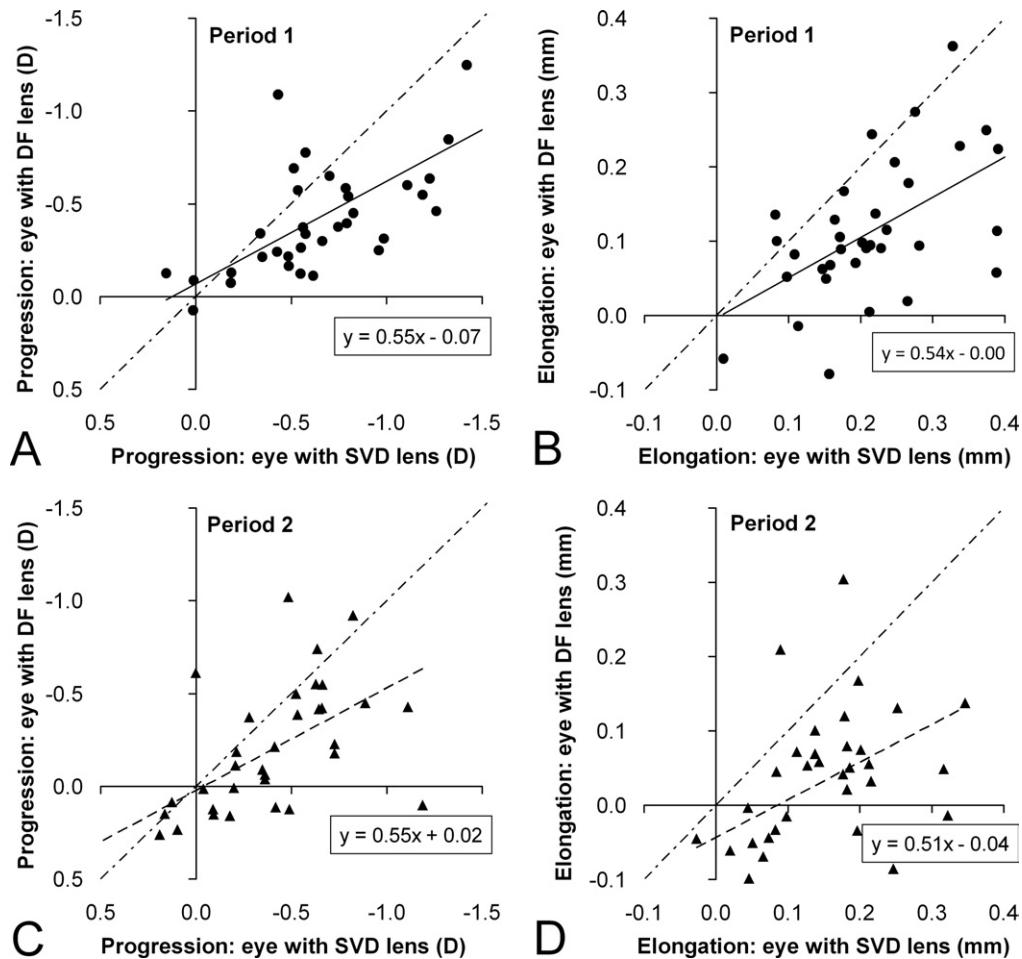


Figure 5. A, B, Period 1. Filled circles show myopia progression (A) and eye elongation (B) in the eye wearing the DF lens plotted against progression/elongation in the eye wearing the SVD lens of the same child during period 1. The diagonal (dot-dashed) lines represent equal progression/eye elongation in the 2 eyes: Solid lines show linear regressions for the data, with the best fitting regression equation given below the abscissa. C, D, Period 2. Filled triangles show myopia progression (C) and eye elongation (D) in the eye wearing the DF lens plotted against progression/elongation in the eye wearing the SVD lens of the same child during period 2. The diagonal (dot-dashed) lines represent equal progression/eye elongation in the 2 eyes: Dashed lines show linear regressions for the data, with the best fitting regression equation given below the abscissa. D = diopters; DF = Dual-Focus; SVD = single vision distance.

numbers of participants are used. The paired-eye design also naturally matches the control and experimental eyes for many other variables reportedly associated with myopia progression, such as age,⁵⁰ gender,³⁴ ethnicity,³⁶ time since myopia onset,⁴⁹ near work,⁵¹ and other environmental⁵² and genetic⁵³ factors. Moreover, during a paired-eye study the rate of progression in each control eye can be used to predict the rate that would have occurred in the treated eye had treatment not been applied. In our study, this allowed efficacy to be investigated across different progression rates as a proportion of that in the control eye (Fig. 5A, B), and participants whose myopia had naturally ceased to progress could be identified. Such comparisons could not be made in a parallel cohort study. However, the validity of such comparisons between experimental and control eye progression relies on the assumption that myopia progression in the 2 eyes is independent. The relatively common occurrence of anisometropia within the population⁵⁴ and the relative ease with which anisometropia can be induced in animals^{24–26}

and humans^{23,31} suggest that the 2 eyes can progress independently, or at least that the interdependence between the 2 eyes is relatively weak. A further advantage of the paired-eye design for our purposes was that it directly tested whether the myopic retinal defocus induced by the DF lens acted to slow myopia progression. Had the lenses been worn binocularly as in a parallel cohort study, it would have been difficult to ascertain whether any effects on progression were due to altered binocular vision status (e.g., an altered convergence-accommodation relationship) or to the direct effect of the myopic defocus itself.

Study Limitations

There are a number of limitations to this study, both with regard to the study design and to the interpretation of the data in period 2. First, the obvious disadvantage of a paired-eye design is that the study of efficacy, tolerability, and so forth is not carried out under the binocular condition in

which the lenses would normally be worn, and therefore the results must be interpreted with caution. A further disadvantage of our study was its short duration. Previous PAL studies have shown small, early beneficial effects that then decrease with time.⁵⁵ Although the underlying rationale for using PALs (to reduce accommodative lag) is different from that for using DF lenses (to present myopic retinal defocus), the duration of the beneficial effect of DF lens wear remains unknown. Our study design also included cross-over of the lens allocation to minimize any treatment-induced anisometropia remaining at the end of the trial. The valid interpretation of results in period 2 (after cross-over) depends on several assumptions, including that the underlying rate of myopia progression remains constant with age and that there are no carry-over or rebound effects after cross-over. Moreover, for the data in period 2 to be fully equivalent to that in period 1, the baseline data (refractions and axial lengths) should be the same at the start of the 2 periods. However, the results of the cross-over analysis described in the “Materials and Methods” showed that significant treatment-by-time and treatment-by-period effects were present, indicating a significant departure from the underlying assumptions. It is also apparent from Figure 4A and B that myopia progression occurred in both eyes during period 1 (albeit at different rates in the 2 eyes) so that by the start of period 2, the mean refractions were more myopic, the eyes were longer, and there was some anisometropia compared with the start of period 1. Moreover, as a result of treatment being applied to only 1 eye in period 1, the progression rates and the starting refractions were not the same in the 2 eyes at the start of period 2. The implications are that the interpretation of data from the 2 periods is not equivalent. Although interpretation of period 1 data is unaffected by these considerations, the data from period 2 must be treated with reservations. Nevertheless, the results of the regression analyses (Fig 5) in which efficacy (assessed as the ratio of progression in the treated eye to that in the control eye) was similar for periods 1 and 2 suggest that period 2 data lend support to the period 1 findings.

Lens Design

The lenses were designed with a large central correction zone to provide normal acuity and to stimulate accommodation for near work. However, the inner treatment zone was also designed to be sufficiently close to the center of the lens that it would fall within the confines of the child’s pupil and present a sustained myopically defocused image to the retina, even during near work. The power of the treatment zones (2.00 D) was chosen to be the same as that used in a previous study of spectacle monovision,³¹ which indicated that 2.00 D of sustained myopic retinal defocus slowed myopia progression in children. However, 2.00 D treatment zones may not be optimal for slowing myopia progression, and the parameters of the treatment zones require further study. Children did not use the DF lenses as if they were bifocal contact lenses. Even when wearing a DF lens in 1 eye and an SVN lens in the other eye (to remove the stimulus to accommodate from that eye), children accommodated for near. This result may be similar to the accom-

modative lead reported in children fitted with simultaneous vision bifocal contact lenses when viewing at near,⁵⁶ where accommodative lead was computed relative to the near plane of focus of the lens.

Comparison with Other Methods of Slowing Myopia Progression

Historically, a variety of different methods for slowing myopia progression have been investigated. Comparing their results is complicated by many factors that differ between studies, including ethnicity of the populations, baseline progression rates in the control groups, environmental conditions, duration of the study, and method of measuring myopia progression, all of which can have significant effects on the outcome. However, comparison of results on the basis of percent reduction in myopia progression normalizes for some of the effects, although such comparisons must still be viewed with reservation.

Studies of the efficacy of muscarinic receptor antagonists in slowing myopia progression have shown that atropine can markedly slow myopia progression and eye elongation in children, whereas pirenzepine seems somewhat less effective. For example, Chua et al²³ reported that in children, 1% atropine eye drops (administered to 1 eye) slowed myopia progression and eye elongation by 0.92 D (77%) and 0.40 mm (100%), respectively, over 24 months. In comparison, pirenzepine reportedly reduced myopia progression by 0.27 D (50%) in the first 12 months, but no statistically significant reduction in axial elongation of the eye was found.⁵⁷ The results of the present study imply that DF lenses are less effective than atropine in slowing myopia progression. Comparison with pirenzepine is less straightforward; DF lenses reduced the progression of myopia by 0.25 D (37%) in 10 months (i.e., somewhat less than pirenzepine), but DF lenses were more effective in significantly reducing the axial eye elongation (by 0.11 mm in 10 months, or 49%) compared with pirenzepine. The reductions in myopia progression and eye elongation found in the present study are slightly less than those from a previous study of spectacle monovision in children from our laboratory,³¹ which found reductions in progression and eye elongation of 0.36 D/year (55%) and 0.13 mm/year (42%), respectively, in the under-corrected eye relative to the fully corrected eye. The efficacies reported for previous PAL studies^{13–15} generally corroborate each other (0.18 D [28%] and 0.07 mm [23%] in the first year;¹⁵ 0.26 D [17%] and 0.11 mm [16%] over 2 years;¹³ and 0.31 D [26%] in 18 months¹⁴) and are typically lower than that of the present study.

There is also some evidence that other forms of contact lenses may slow myopia progression. A small case-control study compared myopia progression in 1 pair of identical twins with near esophoria, when 1 twin was fitted with commercially available bifocal soft contact lenses and the other was fitted with standard single vision soft contact lenses.⁵⁸ The twin fitted with the bifocal contact lenses reportedly showed no myopia progression during the first 12 months (+0.13 D refractive change), whereas the twin wearing SVD contact lenses progressed 1.19 D in the same

period. Orthokeratology may also slow myopia progression. Cho et al⁵⁹ reported that orthokeratology caused a significant slowing of eye growth, in terms of the axial length and vitreous chamber depth, in addition to the expected refractive changes. However, progression in the orthokeratology group was compared with progression in a control group of single vision spectacle lens wearers selected from a previous study to match the age, gender, and baseline refractions of the orthokeratology group.

In the present study, a small increase in CP (0.070 D) was observed in both eyes over the course of the study. Similar corneal changes were reported in the Adolescent and Child Health Initiative to Encourage Vision Empowerment (ACHIEVE) study,³² likely because of the introduction of full-time contact lens wear. However, the mean changes in CP in eyes wearing DF lenses and eyes wearing SVD lenses were not different in period 1 or 2. Consequently, the differences in progression rate observed with DF and SVD lenses cannot be ascribed to changes in CP.

In conclusion, the progression of myopia was slowed significantly in eyes wearing DF lenses compared with SVD lenses, whether myopia progression was assessed as change in ocular refraction or elongation of the eye. These results suggest that sustained myopic defocus, even when presented to the retina simultaneously with a clear image, can act to slow myopia progression. Because DF lenses provide normal acuity and contrast sensitivity, they have potential as a relatively safe and effective form of refractive correction that can also retard the progression of myopia. Soft contact lenses are a well-established mode of optical correction; they can be worn for many years, they have a known safety record, and the potential complications of contact lens wear are familiar to practitioners.

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