Four-year Postoperative Results of the US ALLEGRETTO WAVE Clinical Trial for the Treatment of Hyperopia

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ABSTRACT

PURPOSE: To evaluate the long-term refractive stability after LASIK for hyperopia with the WaveLight ALLEGRETTO WAVE Excimer Laser System.

METHODS: All 151 patients enrolled in the 2000-2002 FDA study of the ALLEGRETTO WAVE laser were contacted by the investigators approximately 4 years after study completion to be evaluated for refractive stability.

RESULTS: A total of 127/290 (43.8%) eyes in 68/151 (45%) patients presented for re-examination. Mean time from the examination taken at the 6-month follow-up stability endpoint in the FDA trial (Stability Exam) to the Post-Approval Exam was 3.9±0.39 years (range: 3.2 to 4.9 years). Stability of the manifest refraction spherical equivalent (MRSE) within ±1.00 D or less was seen in 119/127 (93.7%) eyes. Regression of effect of >1.00 D was seen in 6/127 (4.7%) eyes and progression of effect was seen in 2/127 (1.6%) eyes. Weak correlation of refractive changes with keratometry readings were seen in eyes that underwent >2.00 to 4.00 D treatment (R=0.31) and >4.00 D treatment (R=0.33), implying corneal remodeling may have played a role in the refractive change observed.

CONCLUSIONS: Refractive stability within ±1.00 D MRSE after hyperopic LASIK with the ALLEGRETTO WAVE excimer laser was seen in 93.7% of eyes at 3 years after surgery compared with 6-month follow-up, supporting the conclusion in the FDA trial that refractive stability occurred by 6 months postoperatively. Refractive changes associated with keratometry changes were not significant in eyes that underwent ≤2.00 D treatment. [J Refract Surg. 2008;24:S431-S438.]

Literature reports of hyperopic LASIK vary in their conclusions regarding refractive stability. In a report of the NIDEK EC-5000 CXII excimer laser system (NIDEK Co Ltd, Gamagori, Japan), Kermani et al1 showed improved refractive stability after hyperopic LASIK at 1 year with larger optical zones up to 7.0 mm in diameter. Jaycock et al2 reported that significant regression occurred with the Summit Apex Plus laser (Summit Technologies Inc, Waltham, Mass [now defunct]) in 47 eyes examined up to 54 months after surgery. Regression of up to 1.50 diopters (D) was seen and was found to correlate weakly with age. In a study of the Technolas Keracor 117C laser (Bausch & Lomb, Rochester, NY), Esquenazi3 evaluated 125 eyes at 5 years after hyperopic LASIK and found increased regression in eyes with higher treatment amounts and dry eyes. Other reports show regression of effect with shorter follow-up intervals,4 particularly in patients with higher treatment amounts.5

The WaveLight ALLEGRETTO WAVE Excimer Laser System (WaveLight AG, Erlangen, Germany) received approval of a Premarket Application (PMA) by the United States Food and Drug Administration (FDA) in 2003 for the treatment of up to +6.00 D spherical equivalent refraction hyperopia with up to 5.00 D astigmatism measured at the corneal plane, using LASIK. To evaluate refractive stability after hyperopic LASIK with the ALLEGRETTO WAVE, the investigator group...
recalled the patients enrolled in the FDA study for a Post-Approval Examination in 2006. This study reports the findings.

**PATIENTS AND METHODS**

**STUDY DESIGN**

The study is a post-completion recall of patients enrolled in the prospective, 10-center FDA Investigational Device Exemption (IDE) study. The recall was performed under a protocol that stipulated the following null hypotheses:

- The manifest refraction will become more hyperopic and will correlate with
  - Patient age: older patients will experience less change than younger patients.
  - Difference between correction amount and the preoperative cycloplegic refraction: the greater the difference, the greater the shift in manifest hyperopia.
  - Correction amount: corrections >-4.00 D will show greater change in manifest refraction than lower corrections.

Study investigators were requested to contact study patients and request that they present for examination. Data were collected using clinical data entry forms provided by the FDA study sponsor (SurgiVision® Consultant Group Inc, Scottsdale, Ariz). Participation by both the investigators and patients was voluntary and no compensation was provided for participation in the project.

**CLINICAL OUTCOMES MEASURES**

Findings at the Post-Approval Exam were compared to the manifest and topographic data from the FDA trial at the 6-month examination, which was reported as the “time point of stability” in the PMA Summary of Safety and Effectiveness of the Device.6

Manifest refraction and topographic simulated keratometry readings were used to evaluate refractive and keratometric stability, respectively. The topographer used in all cases was the WaveLight Allegro Analyzer (WaveLight AG). Mean keratometry values (the average of the steep and flat K readings) were used to evaluate changes in keratometry over time. This approach was justified as most eyes had spherical or nearly spherical keratometry readings after surgery. As noted below, analysis was also performed of steep and flat keratometry readings to confirm the validity of this approach.

Manifest refractions were performed according to the methods described in the FDA Study Protocol, which required plus-to-blur and fogging techniques to confirm the endpoint of the sphere refractions.

Stratification of eyes by preoperative refractive range was performed using the manifest preoperative refraction, as reported in the FDA data. Evaluation of the difference between the preoperative manifest and cycloplegic refractions was also done based on the FDA reports.

**STATISTICAL ANALYSIS**

Refractions were converted to the corneal plane for calculation and were evaluated based on the manifest spherical equivalent refraction. Changes in refraction and keratometry were computed for each eye using paired observations prior to inclusion in statistical analysis. Evaluation of mean changes was performed using a paired Student t test. Statistical significance was accepted at the 95% confidence interval (P<.05). Correlations were performed using Pearson correlations. In contrast to P values, which imply increased significance as numbers approach zero, Pearson correlation coefficients indicate stronger correlations when they approach one and weaker correlations as they approach zero.

Statistical computations were performed using the Refractive Surgery Consultant software (Refractive Consultant Group Inc, Scottsdale, Ariz) and Excel (Microsoft Inc, Redmond, Wash).

**SUMMARY OF SURGICAL TECHNIQUE AND ABLATION CHARACTERISTICS**

All treatments performed in this study were conducted under protocol in the FDA study described above. Microkeratomes were not standardized in this study and outcomes were not evaluated according to keratome for this report; however, in the FDA application no difference in outcomes was found for different keratomes. The protocol requirement for the flap required a diameter >8.5 mm and predicted post-ablation stromal thickness of >250 µm.

In this study, determination of the treatment amount was done by the investigator according to the protocol, which allowed for, but did not require, treatments of up to the full cycloplegic amount. Effects of this practice are analyzed below.

All treatments in this series were performed using an optical zone of 6.5 mm and an overall treatment zone of 8.5 mm in diameter. The ALLEGRETTO WAVE uses a wavefront-optimized ablation. The term “wavefront-optimized” refers to an ablation profile that attempts to maintain the preoperative ratio of central to mid-peripheral curvatures after surgery and to provide a refractive treatment that extends to the extent of the nominal optical zone. The ablation outside the optical zone is referred to as the “transition zone.” It gradually shallows the ablation depth to the untreated peripheral cornea. In this series, all ablations were performed using the ALLEGRETTO eye tracker centered on the pupil centroid.
SUMMARY OF FDA STUDY RESULTS
Refractive stability was demonstrated in the FDA study described above at the 6-month postoperative time point, indicating that the refractive change between the 3- and 6-month postoperative intervals was <0.33 D/month in ≥95% of eyes.7 From 1 month to 3 months postoperative, the mean change in spherical equivalent refraction was +0.12±0.40 D. From 3 months to 6 months postoperative, the mean spherical equivalent refractive change was +0.01±0.37 D.

Of the 290 eyes enrolled in the FDA study, 260/290 (89.6%) were examined at the 6-month postoperative time point and were used as the basis for the report of safety and effectiveness of the device. At 6 months, 72.3% of patients were within ±0.50 D of the intended correction and 90.4% were within ±1.00 D of the intended correction. These outcomes exceeded the FDA requirements for PMA approval (Table 1).

RESULTS

COMPARISON OF COHORT TO NON-REPORTED EYES
Key pre- and postoperative data were compared for eyes that presented for the Post-Approval Exam to those that did not, to evaluate for sampling bias. No significant differences were found for sex, preoperative spherical equivalent refraction, postoperative spherical equivalent refraction, or error in postoperative spherical equivalent refraction from the targeted outcome. Results of the comparison are shown in Table 2.

PREOPERATIVE REFRACTIVE CHARACTERISTICS
The mean preoperative manifest spherical equivalent for the eyes reported in this series was 2.20±1.41 D.
Long-term Hyperopic Results With the ALLEGRETTO WAVE/Kezirian et al

Comparison of the preoperative manifest to the cycloplegic spherical equivalent refraction showed that not all eyes were treated for the full cycloplegic amount (Fig 2). A strong positive correlation was noted for younger patients to receive less treatment than their full cycloplegic refractive error (R²=0.98 using a second-order polynomial regression). Potential effects of the untreated (latent) hyperopia are considered below.

REFRACTIVE CHANGES

The mean change in postoperative manifest refraction spherical equivalent (MRSE) from the time point of stability of 6 months after surgery to the Post-Approval Exam was 0.19±0.53 D (Fig 3). One hundred nineteen of 127 (93.7%) eyes were stable within 1.00 D and 6/127 (0.5%) experienced a hyperopic shift of >1.00 D over this interval. When stratified into 2.00-D groupings according to spherical equivalent treatment amount, the change in MRSE was similar for all groups (Fig 4).

Correlations were performed to evaluate for influences on refractive stability. Age, treatment amount, the difference between the preoperative cycloplegic refraction and the MRSE, preoperative keratometry, keratometry at stability, and change in keratometry were all evaluated.

For the overall group, all correlations were weak (R²<0.2), with the strongest correlation found for the change in mean keratometry values between the stability and Post-Approval Exam. In an attempt to isolate trends in each refractive subgroup, the same correlations were performed for each 2.00-D subgroup according to spherical equivalent refraction. In this analysis, it was found that the positive correlation of the change in MRSE between the 6-month and Post-Approval Exam with the change in mean keratometry over the same interval strengthened in the higher ranges. The R value for this correlation was 0.05 for the 0 to 2.00 D group, 0.31 for the >2.00 to 4.00 D group, and 0.33 for the >4.00 D group. Notably, the correlations of the change in MRSE did not trend with age, the mean K at stability, or the difference between the preoperative manifest and cycloplegic amounts.

Figure 1. Preoperative refractive distribution of the eyes in this series (N=127). Most (58%) had refractive errors of ≤+2.00 D, and only 11% had a preoperative spherical equivalent refraction >+4.00 D.

Figure 2. Differences (mean±standard deviation) between the preoperative cycloplegic refraction and the amount treated, stratified by age, in decades (N=127 eyes). Note. Not all eyes were treated for the full cycloplegic refractive error.
Table 3 provides a data line listing of the eyes that experienced >1.00 D change in MRSE from the 6-month Stability Exam to the Post-Approval Exam. No clear pattern accounting for the change was identified.

Astigmatism was similarly stable. At the 6-month Stability Exam, the mean cylinder amount was 0.36±0.38 D. At the Post-Approval Exam, the mean astigmatism was 0.41±0.39 D (P>.05, paired Student t test). No eye experienced >1.00 D of change in refractive cylinder magnitude from the 6-month exam to the Post-Approval Exam, and 116/127 (91.3%) were stable within ±0.50 D.

**Figure 3.** Distribution of the change in A) manifest refraction spherical equivalent (MRSE) and B) mean keratometry readings from the time point of stability in the FDA study to the Post-Approval Exam (N=127 eyes). Positive numbers indicate a hyperopic shift. The mean change in MRSE was 0.19±0.53 D and 93% of eyes were stable within ±1.00 D. The rate for change in MRSE of ±0.50 D was 75% (not shown). The average change in mean keratometry was +0.03±0.78 D with 84.2% stable within ±1.00 D. Change in mean keratometry of ±0.50 D or less was found in 66.7% of eyes (not shown).

**Change in Mean Keratometry**

Mean keratometry values averaged 44.90±2.32 D at the 6-month postoperative examination and 44.94±2.27 D at the Post-Approval Examination (P>.05). The change in mean keratometry readings per eye was 0.03±0.78 D, and 20/127 (15.8%) eyes showed a change in mean keratometry values of >1.00 D. Data stratification did not reveal a significant trend for flattening of keratometry in higher treatment ranges (Fig 4), despite the finding noted above that refractive changes tended to correlate more strongly with change in keratometry in eyes with higher treatment amounts.

**Evaluation of Null Hypotheses**

The general hypothesis that the manifest refraction would become more hyperopic was supported by the data. The mean MRSE was −0.12±0.73 at the Stability Exam and +0.18±0.77 at the Post Approval Exam (P<.001) for an overall mean change in MRSE of 0.19 D.

Data to support the hypothesis that older patients would experience less refractive change than younger patients were evident, but not conclusive. Change in MRSE correlated only weakly with age (R=0.15). Stratification of change in MRSE by decade showed that eyes in patients over 60 years had statistically less change in MRSE than eyes in patients under 60 (0.01±0.26 D vs 0.22±0.56 D, P<.02), but the differences between the decades from 30 to 60 were not significant (not shown). The 4/127 (3%) eyes from patients aged <30 years showed more hyperopic drift (0.50±0.35 D) than the rest of the group (0.18±0.54 D) but the difference was not statistically significant.

The hypothesis that the difference between correction amount and the preoperative cycloplegic refraction would predict changes in MRSE was not
DISCUSSION

This series shows excellent refractive and keratometric stability over 3 years after LASIK treatments for hyperopia with the ALLEGRETTO WAVE Excimer Laser System. The mean change in MRSE was +0.19±0.53 D, with 93.7% of eyes showing stability within ±1.00 D from the 6-month postoperative examination and 75% stable within ±0.50 D (see Fig 3). Mean keratometric readings showed similar findings, with a mean change of 0.03±0.78 D, with 84.2% eyes stable within ±1.00 D and 66.7% stable within ±0.50 D (see Fig 3).

The baseline data for this study were collected as part of the FDA IDE study that led to PMA approval of the ALLEGRETTO laser for LASIK treatments of hyperopia for up to 6.00 D spherical equivalent refraction with up to 5.00 D of astigmatism. The time point of stability in that trial was determined as the Month 6 postoperative examination, indicating that stability was demonstrated between the Month 3 and Month 6 intervals according to the definitions set forth in the FDA Guidance for excimer laser studies. The Post-Approval Exam data presented here were collected 3.9±0.39 years (range: 3.2 to 4.9 years) after the Month 6 exam. The data suggest that the selection of the Month 6 exam as the time point of stability was justified through 4.5 years after surgery.

The results in the FDA study met or exceeded the

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CRSE = cycloplegic refraction spherical equivalent, MRSE = manifest refraction spherical equivalent, K= keratometry

*No clear pattern accounting for the change was identified.

Figure 4. Mean and standard deviation of change in MRSE from 6 months to ~4 years for 2.00-D subgroups (N=127 eyes). The differences between groups were not statistically significant.

TABLE 3

Data Line Listing For Eyes That Experienced More Than 1.00 D Change in Manifest Refraction Spherical Equivalent Between the 6-Month Stability Examination and the Post-Approval Examination*

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The correlation coefficient for this relationship was only R=0.05, suggesting no correlation. The correction amount also did not correlate with changes in MRSE (R=0.04). Stratification of eyes into 2.00-D spherical equivalent refraction treatment groups did not reveal any tendency for greater instability of the MRSE in higher treatment amounts (Fig 5).
Long-term Hyperopic Results With the ALLEGRETTO WAVE/Kezirian et al

FDA requirements for approval (Table 1) and were similar to those reported in a 1-year follow-up study for hyperopic LASIK with the ALLEGRETTO by Kanellopoulos et al. In addition to the visual and refractive results that were reported in the FDA study, the Kanellopoulos study reported higher order aberrations and found that no significant increase in aberrations was encountered in low and moderate hyperopic treatments of up to 5.00 D.

Four general null hypotheses were established prior to conducting this Post-Approval study. The first, that the overall trend would be for increased hyperopia over time, was supported. The mean change of $+0.19 \pm 0.53$ D was statistically significant, however, only 6/127 (4.7%) eyes experienced regression of $>1.00$ D. The second hypothesis that older patients would experience less hyperopic shift than younger patients was supported in patients aged 60 years and older only. The correlation between refractive change and age was generally weak ($R=0.15$).

The third hypothesis proposed that changes in MRSE would be explained by untreated latent hyperopia, ie, failure to treat the full cycloplegic refractive error. There were several eyes in this series where the treatment amount was less than the preoperative cycloplegic amount. As might be expected, this tended to occur in younger patients who had not yet manifested their full hyperopic refractive error (see Fig 2). However, there was no significant correlation between the change in MRSE from the Month 6 to the Post-Approval Exam to the untreated hyperopia, a finding that disproved the null hypotheses. In fact, there was no clear explanation for the eyes that experienced $>1.00$ D of change in MRSE (Table 3).

The final hypothesis, that changes in MRSE would be greater in eyes that had higher corrections, was not proven. Refractive changes over time did not correlate with treatment amount, nor did they correlate with pre- or postoperative keratometry values. However, refractive changes correlated weakly with keratometric changes, particularly in eyes with treatments $>2.00$ D, indicating that loss of refractive effect was caused—at least in part—by changes in corneal curvature. Still, the strongest correlation coefficient, found in eyes with $>4.00$ D spherical equivalent refraction treatment, was only 0.33, suggesting other factors were involved.

Astigmatic stability in this series was remarkable. No eye experienced $>1.00$ D of change in refractive cylinder magnitude from the month 6 to the Post-Approval Exam, and 116/127 (91.3%) were stable within $\pm 0.50$ D.

Keratometry is at best a rough measure of corneal power and may not fully reflect corneal surface remodeling after hyperopic LASIK. Keratometry measures the corneal curvature approximately 3.2 mm from the corneal apex and changes at other points are not described by keratometry measurements. Future studies might consider using of volumetric analysis with corneal tomography to better simulate the association between corneal remodeling and refractive changes after hyperopic surgery.

The use of mean keratometry values to assess keratometric changes, rather than the steep K value, which determines the sphere correction amount and is not affected by astigmatic treatments, is justified because most eyes were left with nearly spherical keratometry values after surgery.

Prior studies have reported various amounts of loss of refractive effect after hyperopic LASIK. Others report refractive stability after surface treatments. This is the first report of refractive stability after hyperopic LASIK with the ALLEGRETTO WAVE Excimer Laser System, and the only report that uses FDA study data as the baseline. The findings in this series suggest that...
Long-term Hyperopic Results With the ALLEGRETTO WAVE/Kezirian et al

Hyperopic LASIK is a reasonable treatment modality with this platform and can provide stable refractive outcomes over time within the approved treatment range of up to 6.00 D spherical equivalent refractive error.

REFERENCES