**Progressive lamina cribrosa deformation – A biomarker for fast progressors in glaucoma?**

**Principal Investigator: Prof. LEUNG Kai Shun, Christopher**

**Co-I: Dr. LEE Wai Yip, Jacky**

**Dr. LI Chi-hong, Felix**

**Dr. CHEN Lijia**

**Background of research**

***Why do we need a biomarker for fast progressors?*** Glaucoma is a chronic, irreversible blinding disease characterized by optic nerve head (ONH) excavation, neuroretinal rim loss and retinal nerve fiber layer thinning. With an estimated number of 21.8 million of glaucoma patients in China by 2020,10 the need to identify progressing patients for treatment is pressing. Nevertheless, a number of landmark glaucoma clinical trials indicate that a considerable proportion of glaucoma patients do not have observable disease progression over years even without treatment. The Early Manifest Glaucoma Trial randomized 129 newly diagnosed open-angle glaucoma patients to intraocular pressure (IOP) lowering treatment (argon laser trabeculoplasty and topical betaxolol 0.5% b.i.d.) and 126 patients to observation.1 Over 6 years of follow-up, 38% of patients in the control group were found to have no identifiable visual field (VF) or ONH progression. In the Collaborative Normal-Tension Glaucoma Study, 66 normal-tension glaucoma patients (defined by the study as having an average IOP ≤20mmHg, with no measurement >24mmHg) were randomized to 30% IOP reduction by medical, laser or surgical means, and 79 patients were randomized to observation.2 Remarkably, 50% of patients in the observation arm showed no identifiable progression over 5 to 7 years and the rate of glaucoma progression was highly variable among the progressors. Given the fact that treatment related adverse effects are common,5-8 these clinical trials underscore the importance of targeting treatment to patients at risk of progression. While analyzing the risk of progression (e.g. the level of IOP, age, disease severity) and setting a target IOP are widely adopted in the current practice, the clinical application of target IOP remains unproven by any study to be accurate or effective.3 What is required is a reliable biomarker for future progression behavior. The LC is a connective tissue structure at the ONH formed by layers of interweaving skeins of collagen, elastic fibers and astrocytes through which axons of retinal ganglion cells pass. Proposed to be the primary site of optic nerve damage in glaucoma,11 the ONH represents a strategic location for early detection of disease deterioration behavior. We hypothesize that progressive LC deformation represents a biomarker for fast progressors and that additional IOP lowering treatment given to glaucomatous eyes with detectable LC deformation would be more effective to reduce the frequency of VF progression than those without. In this proposal, LC deformation refers to posterior displacement of the anterior lamina cribrosa surface.

***ONH and LC deformation precedes functional loss and RNFL thinning: what is the evidence? Experimental evidence*** Experimental studies have shown that ONH and LC changes can be observed before detectable RNFL thinning and reduction in visual function. Strouthidis et al imaged the ONH with confocal scanning laser ophthalmoscopy (CSLO) and RNFL with spectral-domain optical coherence tomography (SDOCT) in 9 rhesus macaques and found that at the onset of CSLO-detected ONH surface depression (at 1.2-5.8 months following induction of experimental glaucoma), there was no significant change in RNFL thickness.12 Significant RNFL thinning was only detected at 7.1-14.0 months. Two recent studies by Fortune et al confirmed this observation with 33 and 68 rhesus macaques using the same imaging instruments.13,14 It is worth noting that CSLO-detected ONH surface depression may represent posterior displacement of the lamina cribrosa, posterior displacement of pre-laminar surface, loss of the neuroretinal rim, loss of the prelaminar tissue or a combination of the above. Hence, CSLO is not able to discern the individual components of ONH deformation. On the other hand because SDOCT provides histological-like details of the retina and ONH with *in vivo* imaging, it is invaluable in visualizing the LC and measuring its deformation. He et al measured the anterior lamina cribrosa surface depth (ALCSD) with SDOCT in 8 rhesus macaques and showed that detectable ALCSD change preceded detectable RNFL thinning and deterioration in visual function (measured by multifocal electroretinography).15 These experimental studies provide substantive data indicating that there is a time lag between ONH/LC deformation and loss in visual function and RNFL in experimental glaucoma. ***Clinical evidence***At least three longitudinal studies have demonstrated that progressive ONH change detected by stereophotography or CSLO occurs before development of identifiable visual field progression in glaucoma patients. Medeiros et al showed that progressive optic disc changes identified by stereophotographs was a strong predictor with a hazard ratio of 25.8 (95% confidence interval: 16.0-14.7) for development of VF defects in glaucoma suspects.16 Chauhan et al. reported that eyes having visual field progression in patients with open-angle glaucoma were 3 times more likely to have prior ONH surface change detected by Topographic Change Analysis.17 In a recent study, we followed 146 eyes of 90 glaucoma patients and imaged the ONH with CSLO and RNFL with SDOCT 4-monthly for at least 4 years to investigate the temporal relationship between ONH surface depression and RNFL thinning.4 Among the 23 eyes demonstrating both ONH surface depression and RNFL thinning at the latest follow-up visit, 19 (82.6%) had ONH surface depression detected before RNFL thinning and the median lag time was 15.2 months. For eyes with concomitant ONH surface depression, RNFL thinning and VF loss, ONH surface depression always preceded VF progression. These studies support the notion that ONH deformation may well serve as an early biomarker for disease deterioration behavior and that a time window is available for therapeutic intervention in many patients upon detection of ONH deformation, before further loss of the visual field and RNFL.

***Pilot data on measurement of progressive LC deformation with SDOCT in glaucoma patients*** In the proposed study, we will use SDOCT to measure LC deformation (anterior LC surface depression) instead of using CSLO to measure ONH deformation (prelaminar surface depression) (FIG.1A-C). This is because SDOCT measured LC deformation commonly preceded or coincided with CSLO ONH deformation in experimental glaucoma.15 With a higher axial resolution, SDOCT has the potential to detect ONH changes earlier than CSLO. In a pilot study, we measured the longitudinal changes of anterior lamina cribrosa surface depth (ALCSD) and prelaminar surface depth (PSD) in 93 glaucoma patients followed for a mean of 4.7 years (FIG.1).18 We showed that ALCSD change was positively associated with PSD change (R2=0.73, p<0.001) and that a higher average IOP during the follow-up period was significantly associated with posterior displacement of the anterior LC surface (p=0.021). For each mmHg increase in the average IOP during the follow-up, the anterior LC surface displaced posteriorly by 2.3µm. Our pilot study indicates the feasibility of using SDOCT for measurement of progressive LC deformation in glaucoma patients (FIG.1D-E) and supports the need of a clinical trial to investigate whether lowering the IOP in eyes with progressive LC deformation would be more effective to reduce the frequency of VF progression compared with those without LC deformation.

***Novelty and impact*** If the objective of the proposed study is achieved, the clinical practice of glaucoma management will be transformed. We would be able to specifically target patients at risk of progressive functional loss for treatment with reference to a novel biomarker for progressors – LC deformation, and minimize costs and treatment associated adverse effects consequential to treating non-progressing patients. Progressive LC deformation may well serve as a biomarker for further VF progression. The demonstration of the adoption of structural endpoints for evaluation of the effect of glaucoma treatment on visual function would be novel and this will impact future clinical trial design for development of new glaucoma treatment.

**2(b) Research plan and Methodology**

The study is complied with ICH-GCP. This is a 2-year prospective, multicenter, randomized treatment trial with a primary objective to test whether glaucomatous eyes (receiving not more than one topical IOP lowering medication at the time of recruitment) with observable progressive LC deformation randomized to additional treatment (IOP reduction) have a greater absolute risk reduction (ARR) of VF (primary outcome measure) and RNFL (secondary outcome measure) progression (i.e. the difference in the proportion of eyes with VF/RNFL progression between the additional treatment and continued treatment groups) compared with those without progressive LC deformation randomized to the same manner (Fig.2). In other words, we expect ARR (LC deformation) > ARR (no LC deformation). Eyes without progressive LC deformation are also randomized because they may also demonstrate further VF progression independent of LC deformation and respond to IOP lowering treatment. The comparison between ARR (LC deformation) and ARR (no LC deformation) will afford an objective measure to quantify the relative treatment effect on eyes with detectable LC deformation.

The study comprises 2 phases (Fig.2). In ***Phase I (36 months)***, 168 consecutive patients with primary open-angle glaucoma (POAG) have been followed up at least 36 months) under ongoing study named as “Diagnostic Imaging Assessment in the Evaluation of Glaucomatous Optic Neuropathy” will be recruited at Hong Kong Eye Hospital. Eyes with progressive LC deformation detected by SDOCT will be randomized to receive additional IOP lowering treatment or continue the current treatment. For patients without progressive LC deformation, they will be randomized with the same manner. Participants no need to receive extra investigations in Phrase I under this study. As participants have completed examinations under “Diagnostic Imaging Assessment in the Evaluation of Glaucomatous Optic Neuropathy” at Hong Kong Eye Hospital and diagnosed with glaucoma at least 36 months. Recruited participants will enter Phrase II under this study directly. In ***Phase II (24 months)***, patients will be followed 4-monthly for clinical examinations, perimetry and SDOCT imaging. The differences in the proportions of eyes with VF and RNFL progression between the additional treatment and continued treatment arms will be compared between the groups with and without progressive LC deformation (as defined in Phase I) by the end of the study. Eyes with VF progression or reaching any of the end-points (see *Study end-points*) at any time during the study period will be managed accordingly.

***Outcome measures*** The primary outcome measure is the (1) proportion of eyes with VF progression (see *Definition of VF progression*). Secondary measures will include (2) the proportion of eyes with RNFL progression, (3) the rate of change visual field index (VFI), and (4) the rate of change of LC deformation before and after IOP reduction. The risk factors of LC deformation (age, IOP levels (mean and standard deviation during the follow-up, glaucoma severity (baseline VF MD and average RNFL thickness), corneal hysteresis (Ocular Response Analyzer), and other biometric and ocular variables (e.g. axial length and ocular perfusion pressure)) will be investigated.

***Subjects*** POAG patients who have been followed up at least 36 months will be consecutively recruited from ongoing study named as “Diagnostic Imaging Assessment in the Evaluation of Glaucomatous Optic Neuropathy” at Hong Kong Eye Hospital with written informed consent obtained. Eligibility criteria are modified from the EMGT.19 POAG is defined as glaucomatous ONH features (narrowing of neuroretinal rim, thinning of the RNFL, optic disc excavation) with corresponding VF defects (see *Perimetry*) in at least 1 eye, with an open angle on gonioscopy and the absence of other ocular diseases or neurologic condition that can account for VF loss. The ***inclusion criteria*** are: age ≥18 years; best corrected visual acuity (VA) ≥20/40; and POAG diagnosed at least 36 months ; Participants are the ongoing participants under “Diagnostic Imaging Assessment in the Evaluation of Glaucomatous Optic Neuropathy and diagnosed with glaucoma “ study at Hong Kong Eye Hospital and have been followed up at least 36 months.

The ***exclusion criteria*** are: IOP >30mmHg measured at any time points during the baseline visit; high myopia (spherical error<-6.0D); advanced VF loss (VF MD <-12dB in the worse eye) or defects close to fixation (any one of the paracentral points with sensitivity <10dB); inability to perform reliable VF; suboptimal quality of SDOCT images (see *SDOCT imaging*); previous intraocular surgery other than uncomplicated cataract extraction; and diabetic retinopathy/maculopathy.

***Clinical examination*** including VA measurement, slit-lamp biomicroscopy for the anterior and posterior segments, GAT IOP and blood pressure measurements are performed at the baseline and follow-up visits. Dark room indentation gonioscopy with Posner lens, axial length measurement with A-scan biometry, central corneal thickness with ultrasound pachymetry and refraction with Auto-refractor are performed at the baseline and the last follow-up visits. Dilated fundus examination with color optic disc stereophotography is performed at the baseline and then yearly. Corneal hysteresis is measured with Ocular Response Analyzer (Reichert Ophthalmic Instruments) at the three IOP measurement time points at the baseline visit. A waveform score of ≥7 is considered to be reliable for inclusion.20

***Perimetry*** is performed with the Humphrey Field Analyzer II (Carl Zeiss Meditec, Dublin, CA, USA) [Cirrus OCT 4000 (SN) 4000-1012, Cirrus AngioPlex OCT (SN) 5000-50xx]. A reliable visual field test has fixation losses, false positive and false negative errors <20%. Unreliable tests are repeated on the same day. A visual field defect, for study inclusion, is defined as having ≥3 significant (p<0.05) non-edge contiguous points with ≥1 at the p<0.01 level on the same side of horizontal meridian in the pattern deviation plot and classified outside normal limits in the Glaucoma Hemifield test and evident in baseline visit. Two VF tests, separated by at least 30 min., will be performed for each eye at the baseline visit.

***SDOCT imaging*** The ONH is imaged with the Spectralis OCT (Heidelberg Engineering GmbH, Heidelberg, Germany) using 24 radial scan lines, each with 768 A-scans, equally spaced at 7.5° with enhanced-depth imaging. Fifteen images at the same location are obtained and automatically averaged by the built-in software to increase the image signal-to-noise ratio. The radial scans are positioned at the ONH center with the eye-tracking function activated. Follow-up scans are acquired with reference to the scan locations of the registered baseline image. All images included in the study have a signal-to-noise ratio ≥20. The RNFL is imaged with the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) [Cirrus OCT 4000 (SN) 4000-1012, Cirrus AngioPlex OCT (SN) 5000-50xx] using the optic disc cube scan (200x200 pixels). Cirrus HD-OCT is used for measurement of the RNFL because its software for RNFL progression analysis is more mature.21,22 Included Cirrus HD-OCT images have a signal strength of ≥7 without any motion artefacts. Two sets of OCT scans (for both Spectralis OCT and Cirrus HD-OCT) will be obtained for each eye at the baseline visit. ***Measurement of anterior LC surface depth (ALCSD)*** is performed in the Spectralis OCT images using a customized program developed in Matlab R2010a (The MathWorks, Inc., Natick, MA).18 The OCT data sets are exported and the ALCSD is measured with reference to manual detection of the Bruch’s membrane opening (BMO) and the visible anterior LC surface in each of the meridians (Fig.1A-B). ALCSD represents the perpendicular distance from the reference line (a line joining the BMO) to the visible anterior AC surface. The scaling factor (µm/pixel) for each of 24 OCT B-scans is extracted from the built-in software and applied in the customized program for measurement of ALCSD. The average ALCSD of an eye is calculated with reference to the 24 meridians. Each of the delineated vertical distances at the anterior LC surface is weighted in proportion to its distance from the BMO centroid. The weightings are given because the peripheral portion of the laminar surface contains a greater arc and thus is less frequently sampled compared with the central portion.12,15,18

***Progression analyses – Definition of progressive LC deformation*** Progressive LC deformation (i.e. increase in ALSCD) is defined when the differences between the follow-up and each of the baseline average ALCSD measurements (follow-up ALSCD minus baseline ALSCD) are greater than the reproducibility coefficient (which has been calculated with reference to a separate group of 30 glaucoma patients with SDOCT measurement in 4 occasions within a month) and confirmed in a consecutive follow-up visit (i.e. a minimum of 2 follow-up visits are required to confirm progressive LC deformation). ***Definitions of VF progression*** VF progression is defined according to the EMGT (Early Manifest Glaucoma Trial) criteria,23 which is available in in the Humphrey Field Analyzer Guided Progression Analysis (GPA) (Carl Zeiss Meditec) [Cirrus OCT 4000 (SN) 4000-1012, Cirrus AngioPlex OCT (SN) 5000-50xx]. Progression is defined when there are ≥3 points that showed significant change (greater than the test-retest variability) compared with two baseline examinations for at least 2 consecutive tests (i.e. “possible progression” in the GPA). We adopt “possible progression” because “likely progression” (i.e. significant changes are detected for ≥3 consecutive tests) is considered to be conservative and may reduce the sensitivity to detect VF progression.24 ***Definition of RNFL progression*** The Cirrus HD-OCT GPA (Carl Zeiss Meditec) [Cirrus OCT 4000 (SN) 4000-1012, Cirrus AngioPlex OCT (SN) 5000-50xx] is used to analyze serial RNFL thickness maps (200x200 pixels) for detection of RNFL progression as described previously.21,22 In brief, GPA automatically aligns and registers two baseline and follow-up OCT images so that the same superpixel (1 superpixel=4x4 pixels) locations are analyzed for detection of change. The difference in RNFL measurement of an individual superpixel between the baseline and the follow-up RNFL thickness maps is compared with an estimate of test-retest variability of that particular superpixel (proprietary database from Carl Zeiss Meditec) [Cirrus OCT 4000 (SN) 4000-1012, Cirrus AngioPlex OCT (SN) 5000-50xx]. Superpixels with an RNFL measurement difference exceeding the test-retest variability between a follow-up and the first and the second baseline images would be encoded in yellow in the OCT RNFL thickness change map (50x50 superpixels). If the same changes are evident in an additional follow-up image, the superpixels would be encoded in red. In this study, RNFL progression is defined when an area of more than 20 superpixels was detected in red in the RNFL thickness change map.

***Specificity of progression analyses*** We examined the specificities for the above definitions for detection of progressive LC deformation, VF and RNFL progression in 28 normal eyes followed ~4 monthly for perimetry and SDOCT imaging over an average of 4.7 years (range: 3.0-5.7 years). The specificities were 92.9% (95% confidence interval: 76.5%-99.1%), 96.4% (95% CI: 81.7%-99.9%), and 94.3% (95% CI: 86.2%-97.8%), respectively.

***IOP lowering treatment*** will be given to eyes randomized to the additional treatment arm in the following order: prostaglandin analogue (PGA), brimonidine, carbonic anhydrase inhibitor (CAI). For example, if the current treatment is a PGA, the additional treatment will be brimonidine. It has been shown in eyes receiving PGA, the average additional IOP reduction was 20% for brimonidine, and 13% to 16% for CAI.25 For patients who are already on maximum tolerated medications, SLT will be performed with treatment protocol as described previously (360° for 100 applications).26

***Study end-points*** include (1) VF progression; (2) decrease in VA ≥ 2 lines; and (3) IOP>30mmHg on 2 consecutive follow-up visits.

***Statistical analysis***

12 follow-up visits over 36 months would be available for detection of progressive LC deformation at the end of Phase I. Progressive posterior LC deformation will be determined by trend analysis of meridional ALCSD. Progressive posterior LC deformation is confirmed when ≥1 meridional ALCSD from any one of the six meridians (the optic nerve head is longitudinally imaged using 6 equally-spaced radial B-scans by the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) with image registration) demonstrates a significant negative trend (i.e. rate of change of ALCSD <0μm/year with p<0.05) for the 2 most recent visits by the end of Phase I. ALCSD will be measured with reference to the choroid sclera interface (CSI). In a recent study (Ref.2), we showed that ALCSD measured with reference to the CSI is less susceptible to the influence of age-related or disease-related choroidal thinning in glaucoma patients.

***Sample size calculation*** Our pilot data indicate that ~50% of eyes showed progressive posterior LC deformation in at least one meridian over ≥ 3 years od follow-up. The randomization of 84 patients to treatment continuation (i.e. a total of 168 patients) would have a power of 82.1% at a 2-sided significance level of 5% to detect a difference of 20% in absolute risk reduction of visual field progression between the groups.

***Potential concerns and solutions: (1) Issues related to patients randomized to receive continued treatment*** Although patients randomized to continued treatmentare followed without additional treatment during the study period, the study would ensure safety for these patients. For example, we will only include patients with mild and moderate damage (MD<-12 dB in the worse eye) and they are followed frequently (every 2-3 months) for clinical examination and investigations. Eyes showing evidence of VF progression or reaching any of the end-points (as mentioned above) in anytime during the study period will receive treatment. ***(2) Recruitment of 168subjects within 12 months*** Study site serving a population of over 2 million with daily outpatient attendance of >3000 will contribute to the recruitment. It is likely that the recruitment can be completed within the study time frame. ***(3) Differences in instruments and algorithms of progression analysis*** may introduce bias into the detection of the relative onset of LC deformation, VF and RNFL progression. We minimize this potential bias by adopting and standardizing the approach of event analysis: two baseline and at least two follow-up visits are required to confirm change in all progression analyses. Notably, all progression analyses showed comparably high specificities (>90%) (see *Specificity of progression analyses*). ***(4)*** ***Stability of BMO reference plane*** The BMO has been shown to be a relatively stable anatomical location for ALCSD measurement. He et al compared the BMO reference plane with another Bruch’s membrane based reference plane for measurement of ALCSD and found that the BMO reference plane had superior sensitivity and specificity for detection of glaucoma onset.15 Reis measured the anterior laminar displacement using the BMO reference plane and a reference plane based on the peripheral internal limiting membrane and reported no significant differences between the two.27 While we adopt the BMO reference plane in the current study, we are prepared to measure ALCSD using other reference plane(s). ***(5) Visible anterior LC surface may change as glaucoma progresses*** which can confound the measurement of LC deformation. Of note, in our pilot study,18 we compared the distance of the visible anterior LC surface at the baseline and latest follow-up visits (followed for a mean of 4.7 years) and detected no significant difference. ***(6)*** ***Anterior displacement of LC*** While it is plausible that expansion of neural canal opening can taut the LC to displace anteriorly during the course of glaucoma progression, we only randomize patients for treatment/observation upon detection of posterior displacement of the anterior LC surface. The significance of anterior displacement of LC in relation to glaucoma progression will be addressed in another study. ***(7) Effect of age on LC deformation*** The degree of LC deformation could be age-related.28 Likewise, the ocular biomechanical properties may influence the degree of LC deformation. Risk factors of LC deformation including age, corneal hysteresis and other biometric variables will be investigated (Objective 3). Adjustment of biometric variables will be considered in the comparison of ARR between the groups with and without progressive LC deformation. ***(8)*** ***LC may continue to deform despite IOP reduction*** and result in VF progression in the treatment group. We will measure the rate of change of LC deformation (Objective 2) before and after treatment and determine the rate of change of LC deformation at which VF progression occurs. A follow-up study will be conducted to investigate if the rate of change of LC deformation can serve to guide and direct the intensity of glaucoma treatment. ***(9) Quality of life and cost-effectiveness analyses*** are not included in the study as the maximum funding amount of General Research Fund (GRF) would not be sufficient to cover these analyses. We will solicit additional funding support for these studies once the GRF is secured.

REFERENCES

1. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M; Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120:1268-79.

2. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol. 1998;126:487-97.

3. Anand N. Target intraocular pressure. 2014 In: Shaarawy T, Sherwood MB, Hitchings RA, Crowston JG, editors. Glaucoma: Medical diagnosis and therapy. 2nd ed. Saunders Ltd.

4. Xu G, Weinreb RN, Leung CK. Optic Nerve Head Deformation in Glaucoma: The Temporal Relationship between Optic Nerve Head Surface Depression and Retinal Nerve Fiber Layer Thinning. Ophthalmology. 2014. In press

5. Fechtner RD, Godfrey DG, Budenz D, Stewart JA, Stewart WC, Jasek MC. Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. Cornea. 2010;29:618-21.

6. Ghosh S, O'Hare F, Lamoureux E, Vajpayee RB, Crowston JG. Prevalence of signs and symptoms of ocular surface disease in individuals treated and not treated with glaucoma medication. Clin Experiment Ophthalmol. 2012;40:675-81

7. Christakis PG, Tsai JC, Kalenak JW, Zurakowski D, Cantor LB, Kammer JA, Ahmed II. The Ahmed versus Baerveldt study: three-year treatment outcomes. Ophthalmology. 2013;120:2232-40.

8. Edmunds B, Thompson JR, Salmon JF, Wormald RP. The National Survey of Trabeculectomy. III. Early and late complications. Eye (Lond). 2002;16:297-303.

9. Weinreb RN, Kaufman PL. Glaucoma research community and FDA look to the future, II: NEI/FDA Glaucoma Clinical Trial Design and Endpoints Symposium: measures of structural change and visual function. Invest Ophthalmol Vis Sci. 2011;52:7842-51.

10. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006;90:262-7.

11. Quigley HA, Addicks EM, Green WR, et al. Optic nerve damage in human glaucoma. II. The site of injury and susceptibility to damage. Arch Ophthalmol. 1981;99:635-49.

12. Strouthidis NG, Fortune B, Yang H, Sigal IA, Burgoyne CF. Longitudinal change detected by spectral domain optical coherence tomography in the optic nerve head and peripapillary retina in experimental glaucoma. Invest Ophthalmol Vis Sci. 2011;52:1206-19.

13. Fortune B, Burgoyne CF, Cull GA, Reynaud J, Wang L. Structural and functional abnormalities of retinal ganglion cells measured in vivo at the onset of optic nerve head surface change in experimental glaucoma. Invest Ophthalmol Vis Sci. 2012 Jun 22;53:3939-50.

14. Fortune B, Reynaud J, Wang L, Burgoyne CF. Does optic nerve head surface topography change prior to loss of retinal nerve fiber layer thickness: a test of the site of injury hypothesis in experimental glaucoma. PLoS One. 2013;8:e77831.

2

15. He L, Yang H, Gardiner SK, Williams G, Hardin C, Strouthidis NG, Fortune B, Burgoyne CF. Longitudinal detection of optic nerve head changes by spectral domain optical coherence tomography in early experimental glaucoma. Invest Ophthalmol Vis Sci. 2014;55:574-86.

16. Medeiros FA, Alencar LM, Zangwill LM, Bowd C, Sample PA, Weinreb RN. Prediction of functional loss in glaucoma from progressive optic disc damage. Arch Ophthalmol 2009;127:1250-6.

17. Chauhan BC, Nicolela MT, Artes PH. Incidence and rates of visual field progression after longitudinally measured optic disc change in glaucoma. Ophthalmology 2009;116:2110-8.

18. Wu K, Weinreb RN, Leung CK. Optic nerve head remodeling in glaucoma: A prospective analysis on prelaminar and anterior laminar displacement. Ophthalmology 2014 (accepted for revision).

19. Leske MC, Heijl A, Hyman L, Bengtsson B. Early Manifest Glaucoma Trial: design and baseline data. Ophthalmology. 1999;106:2144-53.

20. Ayala M, Chen E. Measuring corneal hysteresis: threshold estimation of the waveform score from the Ocular Response Analyzer. Graefes Arch Clin Exp Ophthalmol. 2012;250:1803-6.

21. Leung CK, Yu M, Weinreb RN, Lai G, Xu G, Lam DS. Retinal nerve fiber layer imaging with spectral-domain optical coherence tomography: patterns of retinal nerve fiber layer progression. Ophthalmology. 2012;119:1858-66.

22. Xu G, Weinreb RN, Leung CK. Retinal nerve fiber layer progression in glaucoma: a comparison between retinal nerve fiber layer thickness and retardance. Ophthalmology. 2013;120:2493-500.

23. Heijl A, Leske MC, Bengtsson B, et al, EMGT Group. Measuring visual field progression in the Early Manifest Glaucoma Trial. Acta Ophthalmol Scand 2003;81:286-93.

24. Artes PH, O'Leary N, Nicolela MT, Chauhan BC, Crabb DP. Visual field progression in glaucoma: what is the specificity of the guided progression analysis? Ophthalmology. 2014;121:2023-7.

25. Bournias TE, Lai J. Brimonidine tartrate 0.15%, dorzolamide hydrochloride 2%, and brinzolamide 1% compared as adjunctive therapy to prostaglandin analogs. Ophthalmology. 2009;116:1719-24.

26. Katz LJ, Steinmann WC, Kabir A, Molineaux J, Wizov SS, Marcellino G; SLT/Med Study Group. Selective laser trabeculoplasty versus medical therapy as initial treatment of glaucoma: a prospective, randomized trial. J Glaucoma. 2012;21:460-8.

27. Reis AS, O'Leary N, Stanfield MJ, Shuba LM, Nicolela MT, Chauhan BC. Laminar displacement and prelaminar tissue thickness change after glaucoma surgery imaged with optical coherence tomography. Invest Ophthalmol Vis Sci. 2012;53:5819-26.

28. Ren R, Yang H, Gardiner SK, et al. Anterior lamina cribrosa surface depth, age, and visual field sensitivity in the Portland Progression Project. Invest Ophthalmol Vis Sci. 2014;55:1531-9.