Imaging outcomes in clinical trials of treatments for glaucoma

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Currently, all therapies for glaucoma have been licenced on the basis of their ability to lower intraocular pressure (IOP). However, the main outcome of interest to people with glaucoma is vision-related (VR) quality of life (QoL). Instruments measuring VR QoL are unlikely to be sensitive enough to function as the primary outcome for clinical trials,[1] but they remain important as secondary outcomes to capture side-effects of treatment. Although lowering IOP has been shown to slow visual field (VF) loss,[2] IOP is a far-removed surrogate for VR QoL in glaucoma. Furthermore, IOP would obviously be an inappropriate outcome for a trial of a neuroprotective treatment with no effect on IOP. In contrast, the association of VR QoL measures with VF loss and other measures of vision has been established.[3] Measurements of visual function are recognized by regulatory authorities as the appropriate primary outcome measure for clinical trials in glaucoma[4] and the major clinical trials which have evaluated vision function as the primary outcome have used progressive VF loss as the main outcome measure.

VF tests results are recognised to be highly variable, making the detection of change challenging. The low precision leads to the requirement for large trial sample sizes, a long duration of follow-up and frequent repeat VF tests. Before the UK Glaucoma Treatment Study (UKGTS),[2] typical observation periods for trials of visual field preservation in glaucoma

were > 4 years. Long trial duration increases drug development costs and delays bringing new treatments to the patient.

Because of the well-established association between VF loss and imaging-based measurements of glaucoma-relevant structures (such as the peripapillary retinal nerve fiber layer [RNFL] thickness), evidence that imaging can identify progressive glaucomatous damage and the perceived better measurement precision of imaging-based measurements, there has been considerable interest in investigating the potential role of such measurements as surrogate outcomes for clinical trials.

Medeiros reviewed requirements which need to be met for surrogate endpoints to be regarded as valid.[5] These include that the surrogate endpoint must be able to predict the clinically relevant endpoint, in this case progressive VF loss, and the effect of a treatment on the surrogate endpoint must capture the effect of the treatment on the clinically relevant endpoint.

The UKGTS is the only glaucoma trial to assess the vision-preserving efficacy of one disease-modifying drug with both VF and optical coherence tomography (OCT) outcomes. Time-domain OCT (TD OCT) was employed since spectral-domain OCT (SD OCT) was not in widespread clinical use at the time of trial initiation. Although the rate of TD OCT RNFL thinning was a significant predictor of VF loss, it was not able to distinguish the treatment groups.[6] Thus, the condition that the effect of a treatment on the surrogate endpoint should capture the effect of the treatment on the clinically relevant endpoint was not met. The failure of RNFL thickness measurements to capture the treatment effect may have been a consequence of the poor measurement precision of TD OCT, which is known to be lower than SD OCT, resulting in a poor signal-to-noise ratio (SNR). Therefore, we argued that if the

SNR of TD OCT were improved, the RNFL thickness measurements may then be able to capture treatment effects.

In our companion paper,[7] we report a deep learning technique, called super-resolution. The algorithm was trained on TD OCT (Figure, a) and SD OCT (Figure, b) image pairs to convert the TD OCT image to a 'synthesized SD OCT' image (Figure, c). The method was trained and validated on an independent data set and then applied to the UKGTS data set. When applied to the training dataset, the method significantly improved the agreement of segmented TD OCT RNFL thickness measurements with real SD OCT measurements and significantly reduced the test-retest variability. When applied to the UKGTS TD OCT data set, the strength of the predictor 'rate of RNFL thickness loss' for the outcome 'time to incident VF progression' was strengthened: hazard ratio 1.09 (95% CI 1.02 to 1.21) (p=0.035) for TD OCT and 1.24 (95% CI 1.08 to 1.39) (p=0.011) for synthesized SD OCT. Furthermore, measurements of the rate of RNFL thickness loss from synthesized SD OCT images was able to distinguish the UKGTS treatment groups. The mean difference in the rate of RNFL change between the treatment and placebo arms of the UKGTS with TD OCT was 0.24 µm/year (p=0.08; Figure d) and with synthesized SD OCT was 0.43 µm/year (p=0.0017; Figure d) [Mann Whitney U test]. The mean difference in the rate of VF loss (mean deviation, MD) in the same subsample of the UKGTS data set was –0.41 (2.27) dB per year in the placebo group and –0.04 (0.91) dB per year in the latanoprost group (Figure, e-right); (Figure, e-left) shows the original UKGTS data. Thus, we have now been able to show that an imaging outcome captures the treatment effect of IOP-lowering by latanoprost on the primary outcome, progressive VF loss.

We now evaluate the sample size required should RNFL thickness measurements from SD OCT images be the primary outcome in a clinical trial of a glaucoma treatment. Calculating

the sample sizes required to identify a difference between treatment groups with a power of 90% and two-sided significance of 5% from the rates of RNFL thinning illustrated in the figure (d, e), we obtain 4146 for TD OCT and 769 for synthesized SD OCT. For comparison, the sample size required for the rate of MD change, a sample size of 624 is required. The precision of RNFL thickness measurements from synthesized SD OCT images is still inferior to that from real SD OCT images, so it is reasonable to expect that the use of SD OCT in a trial would result in a still smaller sample size.

The results of this work provide evidence that imaging measurements predict the clinically relevant outcome and capture the treatment effect of latanoprost on the VF. In these respects, OCT imaging of the RNFL meets the requirements to be a surrogate outcome. OCT imaging is unlikely to replace the VF as the primary outcome for clinical trials of glaucoma, but these results provide a justification for the development trial designs in which imaging supplements the VF outcome.

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HUMAN SUBJECTS: The UKGTS, and the subsequent analysis of anonymized data in this study, adhered to the tenets of the Declaration of Helsinki and was approved by local institutional review boards (Moorfields and Whittington Research Ethics Committee on June 1, 2006, ethics approval reference, 09/H0721/56). Study participants provided written informed consent.

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