Baseline characteristics of participants in the Treatment of Advanced Glaucoma Study (TAGS): A multicentre randomised controlled trial.

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Key words

Glaucoma, advanced glaucoma, glaucoma surgery, glaucoma drops, Quality of Life, Randomised Clinical Trial, socioeconomic deprivation.

Abstract

Purpose: To report the baseline characteristics of participants enrolled in the Treatment of Advanced Glaucoma Study (TAGS)

Design: Pragmatic randomised control trial (RCT).

Participants: Patients with open angle glaucoma presenting with advanced glaucoma in at least one eye as defined by the Hodapp-Parrish-Anderson (HPA) criteria of severe defect.

Methods Participants with newly diagnosed advanced glaucoma in at least one eye were recruited. When both eyes were eligible, the same intervention was undertaken in both eyes and the index eye for analysis was the eye with the less severe visual field mean deviation (MD).

Main Outcome Measures: Visual field profile defined by the HPA classification, clinical characteristics, Quality of life measured by the National Eye Institute Visual Function Questionnaire 25 (VFQ-25), EuroQual-5 Dimension (EQ-5D 5L), Health Utility Index-3 (HUI-3) and Glaucoma Profile Instrument (GPI)

Results: Four hundred and fifty-three patients were recruited. The mean visual field MD was -15.0dB (SD 6.3) in the index eye and -6.2dB in the non-index eye. Of index eyes (HPA 'severe' classification) at baseline, over 70% had a mean deviation < -12.00dB and nearly 90% had more than 20 points defective at the 1% level. The mean LogMAR visual acuity of the index eye was 0.2 (SD 0.3),

Conclusions: TAGS is the first RCT to compare medical and surgical treatments for patients presenting with advanced open angle glaucoma in a publicly funded health service. It will provide clinical, health related quality of life and economic outcomes to inform future treatment choices for those presenting with advanced glaucoma

Introduction

Glaucoma is a common, chronic, irreversible, optic neuropathy affecting peripheral vision in predominantly older adults(1) . Primary open angle glaucoma (POAG) affects over 2% of those over 40 years(2). It is the second leading cause of blind registrations(3), a major cause of disability in the elderly (4, 5) and worsening of Health-Related Quality of Life (HRQoL)(6-11).

The incidence of POAG is estimated at 11,000 per year in people aged 40-70 in the UK(12, 13). Approximately 1 in 4 patients present with advanced disease(14-18). However, the most recent UK estimate (2006) indicated 39% of newly diagnosed cases had advanced disease in at least one eye(19). Having advanced glaucoma at diagnosis is associated with a higher risk of blindness compared with early stage detection(20-26).

Effective treatment stops or delays disease progression (27-29). The American Academy of Ophthalmology does not specifically recommend a treatment approach for those presenting with advanced glaucoma(30), however, in the UK, the National Institute of Health and Care Excellence (NICE) recommends primary augmented trabeculectomy for patients presenting with advanced glaucoma(13). A recent survey of ophthalmology consultants(31) suggests these guidelines are not commonly adhered to within the UK because of concerns regarding surgery risk and uncertainty about the best primary therapeutic option for such patients. The Treatment of Advanced Glaucoma Study (TAGS) addresses this uncertainty and fulfils a recommendation of a recent Cochrane review(32) to undertake research to determine whether primary medicine or primary surgery is best for patients presenting with advanced glaucoma. TAGS will be the first study to evaluate the best treatment for patients presenting with advanced glaucoma who are those most at risk of developing blindness in their lifetime(20-24).

The primary objective of this report is to characterise the baseline features of the TAGS cohort and further explore the profile of the advanced visual field loss in terms of the Hodapp-Parrish-Anderson criteria of visual field loss.

Methods

TAGS is a pragmatic multicentre randomised controlled trial and the design of the study has been described in detail elsewhere(33). Eligible patients with advanced POAG in either eye were randomised to have augmented trabeculectomy or intraocular pressure (IOP) lowering drops as their primary intervention and followed up for 24 months. Randomisation was based on the participant (not the eye), but for those where both eyes were eligible, clinical outcomes are based on the index eye defined as the eye with better mean deviation (MD) value.

Disease Classification: Eligible patients had primary open angle glaucoma (including pigment dispersion and pseudoexfoliation). Advanced glaucoma was defined according to the Hodapp-Parrish-Anderson (HPA) classification of severe glaucoma(34). At baseline participants eligibility was determined with 2 SITA Standard 24-2 visual field examinations and visual fields in addition to mean deviation value, were graded according to which of the 5 potential criteria defining severe glaucoma according to the HPA grading system they fulfilled.

Interventions: In the primary medical treatment arm, participants start on one or more medications at their initial visit depending upon the judgement of the treating clinician and as advised by the NICE glaucoma guidelines(1) Subsequent additional medications are based on clinician judgement. If drops fail to lower the IOP adequately, oral carbonic anhydrase inhibitors may be used. If medical treatment fails patients will be offered glaucoma surgery. In the primary trabeculectomy group, surgery should be undertaken within three months of randomisation by a surgeon who specialises in glaucoma or a glaucoma fellow who has performed at least 30 trabeculectomies. Patients' IOP will be medically controlled until glaucoma surgery is undertaken. Trabeculectomy will be augmented with mitomycin-C. After glaucoma surgery, medical treatment may be introduced if the IOP is above the desired target.

Outcome Measures: Clinical measurements for visual field loss MD and HPA Criteria on Humphrey visual field testing. Logarithm of the mean angle of resolution (logMAR) visual acuity (VA), IOP. Incidence of blindness(35) at diagnosis, family history of glaucoma and self reported frequency of contact with primary care optometry in years prior to diagnosis. Health Related Quality of Life (HRQoL) generic health status [EuroQual-5 dimension – 5 level (EQ-5D-5L)(36) and Health Utility Index (HUI-3)(37), visual health status [National Eye Institute Visual Function Questionnaire 25 (VFQ-25)](38), glaucoma health status [glaucoma utility index (GUI)](39), patient experience.

Follow-up: In addition to the baseline visit patients will attend 3 scheduled study visits at approximately 4, 12 and 24 months post-randomisation. Clinical data is collected at each of these visits. HRQoL information is collected on self-reported questionnaires at baseline, 1, 3, 4, 6, 12, 18 and 24 months, and participant costs and healthcare utilisation for health economic evaluation are collected at 4, 12, 18 and 24 months. The discrete choice experiment was elicited at 27 months. Study schedule is described in Supplementary Table 1. Where a data collection time was not a clinic visit data was collected via postal questionnaire.

Statistical analysis: Baseline characteristics are described using numbers and percentages for dichotomous variables, numbers, median and interquartile range (IQR) for the number of times the participant visited the optometrist in the last 10 years and mean and standard deviation (SD) for all remaining continuous variables. For participants in whom both eyes were eligible, data are summarised for both the index and non-index eye., In addition, for visual fields MD, better eye (higher MD score) and worse eye (lower MD score) are also reported. For participants who declined to participate in the trial, age and gender were compared with participants randomised using a t-test and chi-squared test, respectively. EQ-5D-5L was calculated following the method by Van Hout et al(41) and GUI was calculated following the method by Burr et al(39) . All analyses were performed in Stata 15 software. (42)

Results

Participant flow

Eligible patients were recruited from 27 secondary care hospital centres in the UK between 3rd June 2014 and 31st May 2017 (Appendix 1). The trajectory of recruitment from all centres is shown in Appendix 2.

There were 951 patients identified to be potentially eligible, of these 453 were randomised. Patients (N=498) were excluded because they were ineligible (N=229) or declined (N=268); for one participant the reason is unknown (Appendix 3). The commonest reason why patients were not eligible was that they could not be randomised in the 3 months window following diagnosis (23%) or the visual fields at a screening visit did not fulfil eligibility criteria (23%). Of those who declined to participate the main reasons were they did not want to have surgery (19%) or lifestyle considerations (16%); over 28% of patients did not indicate why they declined. The reason why two patients were not randomised was not recorded (Appendix 3).

Baseline characteristics

The baseline participant characteristics are shown in Table 1. The mean age of participants was 67 (SD 12.3) years; 303 (67%) of participants were male. For those individuals who declined to participate in the trial (n=265), the mean age was slightly, but statistically significantly, greater than that of participants at 69 (SD 12.8) years (p-value 0.04); 165 (62%) were males (p-value 0.17). Participants were mainly Caucasian (82%)

Primary open angle glaucoma was the commonest form of open angle glaucoma accounting for 97% of the cohort. Advanced glaucoma was present in both eyes in 19.4% of participants.

Baseline patient experience measures are shown in Table 2. The mean VFQ-25 was 87.1 (SD 13.5), the general vision and general health subscales were most affected. For generic health status the HUI-3 scored lower than the EQ-5D-5L at 0.81 and 0.84 respectively and just over one third (37.7%) self-reported that they felt their glaucoma was getting worse. There was a 10dB difference on average between the better eye visual field loss [-5.5 (SD 6.1) dB] and the worse eye visual field loss [-15.7 (SD 6.7) dB] at presentation.

Baseline clinical characteristics for the index and non-index eye are shown in Table 3. The eyes are similar for most measurements. However, the mean VF loss was greater in the index eye (MD = -15.0 dB) compared to -6.2 dB in the non-index eye. Similarly, the IOP was greater in the index eye both at diagnosis and baseline. The mean IOP (mmHg) at diagnosis and baseline was 26.4 and 19.2 respectively in the index eye, and 22.9 and 17.9, respectively, in the non-index eye. Participants were mainly taking prostaglandin analogue drops at baseline, 81.2% in their index eye and 70.6% in their non-index eye. The mean visual acuity was LogMAR 0.2 in the index eye and LogMAR 0.1 in the non-index eye. Binocular visual acuity was LogMAR 0.1 (n =441; SD 0.01). Six percent of the cohort were eligible for sight impairment registration in the UK at the time of diagnosis.

The vast majority of patients were phakic (>90%) and about a fifth had associated ocular co-morbidity.

The HPA criteria leading to a 'severe' classification of glaucoma in the index eye at baseline is shown in Table 4. Over 70% had a mean deviation < -12.00dB and nearly 90% for more than 20 points defective at the 1% level.

Discussion

TAGS was designed to be a pragmatic trial comparing established options, medications or surgery, as initial treatment for people diagnosed with severe glaucoma. Only the primary intervention was dictated by the trial protocol (33).

Recruitment to RCTs comparing surgical and non-surgical interventions can be challenging(43). TAGS recruited to time and to target which may reflect the considerable pre-trial effort to ensure that the trial was conducted in a way acceptable to patients and information presented in a way that was understood(44).

Nearly one third of our cohort reported a family history of glaucoma which is similar to three previous primary intervention studies of patients with early glaucoma(45-47). Suggesting that having a family history of glaucoma does not reduce your risk of presenting with advanced disease.

One mechanism for minimising risk of presentation with advanced glaucoma is a regular visit to an eye care professional. In England, current policy facilitates visits to a community optometrist annually for those over 40 years with a family history of glaucoma. In addition, all people over the age of 60 years are entitled to a free eye test every 2 years. Nearly one third of the participants in TAGS had a known family history of glaucoma (so entitled to annual glaucoma screening) and the vast majority were over 60 years old. The participants report a median of 5 visits to their optometrist in the 10 years prior to diagnosis with advanced glaucoma. These findings suggest that, despite a robust public health provision to prevent diagnosis with advanced disease, a large number of patients are still not being diagnosed at an early stage. Indeed over 6% of the cohort were eligible for sight impairment registration in the UK at the time of diagnosis(35). The reason these opportunities to diagnose glaucoma earlier are missed is unknown. It is possible that participants have some recall bias and over-estimated the frequency of visits to their optometrists prior to diagnosis or that they were rapid progressors as previously suggested by Fraser(48). However, it has also been suggested that delays in diagnosis may occur at several points, from failure of recognition/diagnosis of glaucoma by optometrists, to failure to refer appropriately or delays in this process occurring(49).

One reason this reduced vision may not have prompted patients to seek attention earlier is a resignation among older people that poorer vision is a natural consequence of ageing(52) and they may not therefore pay much attention to the subtle and slowly developing deterioration associated with visual field loss, especially if only affecting one eye .

Visual Field loss

VF damage is the major clinical measure of the functional impact of glaucoma, which adversely influences QoL(8, 9, 54, 55).

There are few RCTS which have explored treatment outcomes in patients with advanced glaucoma and none which have explored primary interventions in a treatment naïve cohort. In the TAGS, the mean visual field MD score of the index eye was -15.0 dB. Although an Advanced Glaucoma Intervention Study (AGIS) has already been undertaken, that study defined 'advanced' as "When maximum effective, accepted, and tolerated medications fail to reduce intraocular pressure adequately and there has been some visual field loss, the patient is said to have advanced glaucoma"(56). In AGIS the extent of visual field loss was not an entry criterion. The MD for the AGIS cohort was not reported as a whole but was about -10.5 dB (mean defect -11.3dB for black participants and -9.4dB for white participants(57). In AGIS, participants had also already exhausted possible medical interventions. The Tube Versus Trab (TVT) study recruited participants with previous surgical intervention and an MD of -16.7 (SD 9.32) dB, however the patients had uncontrolled glaucoma already, despite previous medical and surgical interventions(58). Similarly, the Primary Tube Versus Trab study (PTVT) recruited patients with inadequately controlled glaucoma on maximum tolerated medical therapy but no previous surgery; these patients had an MD of -14.7 dB(59). Neither of these study cohorts examines primary interventions in treatment naïve patients with advanced glaucoma and all tested different interventions compared to those being explored by TAGS.

There have been several previous RCTs of primary medical versus surgical treatment(32). In these, disease severity has been variable, and, since they were undertaken, medical and surgical interventions have evolved. In the Moorfields Glaucoma Trial, the stage of glaucoma was not described(60, 61). In the Glasgow Trial, 35% of participants had severe glaucoma (according to the study definition)(62). In the Moorfields Primary Treatment Trial, 48% of participants had severe glaucoma (according to the study definition >12 absolute defects on Friedman perimetry)(63). In CIGTS, most participants had mild glaucoma based on the average MD of -5.5 dB; one hundred and sixty-eight (27%) participants had no visual field defect, and were included on the basis of IOP >= 27 mmHg and an optic disc appearance compatible with glaucoma. Thus, TAGS is the first and largest cohort of patients with advanced glaucoma evaluated with the Humphrey Visual Field Analyser which will provide a more precise method of evaluation of long-term visual field changes in patients with primary advanced visual field loss.

Two recent RCTs assessing treatment in OAG, the Laser in Glaucoma and Ocular Hypertension Trial (LiGHT)(29)and the United Kingdom Glaucoma Treatment Study (UKGTS)(28) recruited cohorts with mild glaucoma. In the LiGHT, the mean baseline MD for the OHT participants was -1.25 (SD 2.05) dB and for POAG participants was -3.81 (SD 3.68) dB and for UKGTS the median (IQR) baseline VF loss was -2.9 (-1.6 - -4.8) dB so both these cohorts had considerably less baseline VF loss than those entered into TAGS. TAGS, therefore, provides valuable information not already available for patients presenting with advanced visual field loss and complements previously undertaken studies exploring interventions in patients with mild visual field loss.

Quality of Life

Glaucoma is a bilateral disease and the severity of visual field loss in both the more and less affected eyes affects the VFQ-25 score(10, 64). Additionally, central location of visual field(65) loss also decreases HRQoL. For patients with progressive glaucoma, having more advanced binocular loss disproportionately results in more HRQol reduction for each further dB loss of visual field(11). Table 4 demonstrates that both global and localised central defects are well represented in the cohort ensuring that TAGS is uniquely designed to explore further these observations in a large group of patients with advanced glaucoma.

No previous primary treatment RCTs for advanced glaucoma have assessed patients reported outcomes. The Tube versus Trabeculectomy (TVT) study reported the VFQ-25 in patients with advanced glaucoma but these patients had longstanding glaucoma prior to recruitment(66). For the TAGS, the vision specific VFQ-25 composite score was 87.1 (SD 13.5) which is better than the level reported in the TVT study of 71.9 (SD 17.9). This difference may reflect that patients in the TVT study had longstanding glaucoma, had previous incisional surgery prior to recruitment and a mean visual field MD of -16.7dB. As the VFQ-25 is a measurement influenced by bilateral visual function(10, 64), rather than just the index eye visual function, it is possible that patients in TVT with longstanding glaucoma also had worse baseline visual function in the non-index eye.

TAGS is the first study of patients with advanced glaucoma to report values for the generic health status instrument EQ-5D-5L. One previous study of patients with early POAG and OHT (LiGHT), reported an average value of 0.92 (SD 0.13), which is better than that recorded for TAGS of 0.84 (0.18) suggesting a considerable difference in generic HRQoL for patients with advanced glaucoma compared to those with early disease, albeit that the LiGHT cohort were on average about 3 years younger (64.1 vs 67.2) than TAGS patients at baseline. To explore whether including a generic health instrument with a vision specific domain better reflects HRQoL in patients with advanced glaucoma, we also collected data with the HUI-3, which found a small 3 point score reduction compared with the EQ-5D-5L. It is, therefore, uncertain if the HUI-3 incorporating vision disability into its composite score is more effective as a generic HRQoL in patients whose vision is affected. Long term follow-up of the TAGS cohort will provide further insight into which, if any, of these two measurement tools is more effective in capturing change in glaucoma status.

The GUI was used to report glaucoma specific health status. For the GUI in LiGHT, the mean score was 0.89 for the POAG group(47). In TAGS the mean score was also 0.89 (SD 0.12). This suggests a poor ability for the GUI to discriminate between early and late disease, and this may reflect the modest number of people in the reference cohort of GUI development with advanced glaucoma(39). However, this may alternatively be a reflection that there was relatively good function of the non-index eye in many of our cohort, masking this difference.

Although several previous RCTs of primary medication vs trabeculectomy have been undertaken only one collected any patient-reported outcome measures (PROMS)(67, 68). The Collaborative Initial Glaucoma Treatment Study (CIGTS) recruited patients with early glaucoma and collected a battery of PROMS reporting both systemic and local effects of treatment. There was no difference at baseline between surgery and medicine groups in this study(68), however it did not use any of the instruments employed in the TAGS. TAGS is the first study where generic, vision and glaucoma specific PROMS have been collected systematically in patients with advanced disease at presentation and the first glaucoma RCT to report HUI-3, which contains a vision specific domain.

In conclusion, the baseline characteristics of the TAGS cohort show advanced visual field loss is well represented with both global and central visual field loss at baseline. This cohort provides a unique opportunity to establish which primary interventions best preserves the vision of those presenting with advanced glaucoma

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Ethics approval: The study adheres to the tenets of the Declaration of Helsinki and the principles of Good Clinical Practice (GCP), and is in accordance with all applicable regulatory guidance, including, but not limited to, the Research Governance Framework. TAGS' protocol and patient-facing documentation were prospectively reviewed and approved by the Derby 1 Research Ethics Committee (ref number 13/EM/00395). Local NHS Research and Development (R&D) approvals were obtained prior to commencement of the trial at the participating sites. An independent Trial Steering Committee and separate independent Data and Safety Monitoring Committee oversee the trial.

Supplementary Table 1: Outcome Measurements

		Post-randomisation (months)						
	Baseline	1	3	4	6	12	18	24
Clinical								
• Medical History	x							
• Humphrey Visual Field Mean Deviation	x			x		x		x
• Esterman Visual Field	x							x
• LogMAR Visual Acuity	x			x		x		x
• Intraocular Pressure	x			x		x		x
• Standard clinical examination	x					x		x
Patient Experience								

• NEI – VFQ-25	x			x		x		x
• EQ-5D-5L*	x	x	x		x	x	x	x
• HUI-3*	x	x	x		x	x	x	x
• GUI*	x	x	x		x	x	x	x
• Patient experience questions	x	x	x		x	x	x	x
Health economics								
• Health Care Utilisation (including hospital visits)				x		x		x
• Participant Cost				x		x		x
• Participant Time and travel							x	

[a] NEI-VFQ25 – National Eye Institute Visual Function Questionnaire (25 items); HUI-3 – Health Utility Index; GUI – Glaucoma Utility Index; LogMAR – Logarithm of the mean angle of resolution.

* additional questionnaire undertaken immediately prior to trabeculectomy surgery; Discrete Choice Experiment at 27 months;