Testing the Eligibility of Glaucoma Patients for Potential Gene Therapy Among a Clinic Population

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Abstract

Purpose

Glaucoma patients who deteriorate despite standard treatment may benefit from novel gene therapies. Key inclusion criteria for a glaucoma gene therapy trial were devised. A retrospective chart review in a glaucoma clinic population was conducted. Feasibility of gene therapy inclusion criteria and factors associated with progression and fast progression < -1 decibels/year (dB/y) were evaluated.

Methods

374 Primary Open Angle Glaucoma patients all of whom had performed at least 5 Swedish Interactive Threshold Algorithm Standard visual fields within a 58 months period. Two definitions were applied to characterise visual field progression rate using Guided Progression Analysis for an individual patient based on A, the eye with the greatest visual field loss, or B, the eye with the most rapid progression rate.

Results

Mean rate of visual field progression was – 0.50 dB/y (Definition A) and – 0.64 dB/y (Definition B). 19.0% (A) and 21.9% (B) of eyes, 71 (A) and 82 (B) eyes, were 'fast progressors' (< -1 dB/y). 37 (A) and 43 (B) eyes met the putative gene therapy inclusion criteria ($\geq$ 50 years; mean deviation $\leq$ -4 to $\geq$ -12; $\leq$ -20 dB, progression rate between – 1 to -4 dB/y). Beta blockers (Odds ratio (OR) with 95% Confidence Intervals (CI): 2.84 (1.39 – 5.80); p = 0.004) (A), (OR (95%CI): 2.48 (1.30 – 4.75); p = 0.006) (B) and alpha agonists (OR (95%CI): 2.18 (1.14 – 4.17); p = 0.02) (A), (OR (95%CI) 2.00 (1.08 – 3.73); p = 0.028) (B) were significantly associated with fast progression.

Conclusion

A substantial proportion (10%) of patients in this clinic population would meet recommended gene therapy inclusion criteria.

Key Messages

1. Rates of progression of treated glaucoma patients and percentage of 'fast progressors' varies between studies. Inclusion criteria for patients whose glaucoma is progressing 'fast' and who may be suitable for glaucoma gene therapy trials have not been previously defined.
2. By applying key inclusion criteria for a glaucoma gene therapy trial to a tertiary care clinic population to assess the potential for recruitment to a gene therapy trial, 10% of patients would be eligible.

Introduction

Glaucoma is the principal cause of irreversible blindness.[1] Rates of progression in patients under standard care vary between studies.[2–9] The percentage of 'fast progressors' and the threshold defining 'fast progressors' also differs between studies.[7, 4, 6] When visual field loss has occurred, the visual field MD does not ameliorate significantly anymore, despite intraocular pressure IOP lowering treatment.[10] Hence, for cases progressing rapidly despite standard treatment, gene therapy with neuroprotective substances could be beneficial to reduce the risk to lose vision.[11]

Following a consensus between glaucoma specialists, we devised key inclusion criteria for a glaucoma gene therapy trial. Eligible patients would need to be 'fast progressors' with a progression rate between −1 and − 4 dB/y and a most recent visual field (VF) mean deviation (MD) range of -4 dB ≥ MD ≥ -12 dB or ≤ -20 dB. They would need to have a diagnosis of Primary Open Angle Glaucoma (POAG) undergoing standard treatment, and an age threshold of 50 years of age and older was chosen.

Factors which have been reported to be significantly associated with progression in treated glaucoma patients include number of surgeries, age, IOP, MD at study start and central corneal thickness (CCT).[4, 2, 12–14] In the proposed analysis of POAG patients of the Cambridge University Hospital Glaucoma Clinic, not only factors associated with progression, but also factors associated with 'fast progression' at a rate < -1 dB/y were to be identified as they could potentially be used as covariates in recruitment to a gene therapy trial.

Methods

Epic Systems software (Epic, Verona, WI, USA) was used to search for patients who had at least 5 VF orders in the period from October 2014 to July 2019 and the ICD-10 diagnosis H40.1 in the visit diagnosis, problem list or medical history. Patients who had at least 5 VF (24 – 2 SITA Standard, Humphrey Field Analyser III; Carl Zeiss Meditec, Inc, Dublin, California, USA), after subtracting the first ever done VF and at least a 3 years series of VF, were selected. Charts were reviewed to identify and extract patients with the diagnosis of POAG, which was defined by the criteria of open angle, VF defect, optic nerve head changes consistent with glaucoma and absence of secondary glaucoma.

The 58 months timeframe between October 2014 and July 2019 was chosen, since Epic Systems software was implemented in October 2014 at Cambridge University Hospital and all patient records were available since then. The data collection started at the end of July 2019 and therefore surgeries and medical treatments until the end of July 2019 were taken into account.

Glaucoma progression analysis (GPA) and a chart review were conducted. The following variables were recorded: age at the end of the period evaluated, gender, follow up time, total number of VF, MD and Visual Field Index (VFI) at baseline, defined as the first VF that a patient had had in the timeframe, final MD and VFI of the last VF a patient had had in the period evaluated, progression rate in MD (dB/y), progression rate in VFI (%/y), IOP at every visit in the 58 months, number of IOP readings, CCT, treatment

classes of ocular hypotensive agents used, incisional/laser operative interventions. Ethnicity was not included in the analysis, as the majority of patients self-classified as White British according to their charts. The highest IOP at every visit was recorded. As no patient had had refractive surgery in the timeframe, which could have had an impact on the CCT, the final pachymetry reading of the period evaluated (Pachmate 2, DGH Technology Inc., Exton, Pennsylvania, USA) was recorded.

Exclusion criteria were blindness and visual acuity classified as 'Hand Movements' and 'Counting Fingers' at the beginning of the period evaluated. VF with a false-positive rate of more than 15% were excluded. Eyes with significant ocular comorbidity, where the comorbidity might have had an impact on the mean deviation or progression of the VF, were analysed separately and then judged for in/exclusion from the analysis by a glaucoma specialist (RB). The comorbidities excluded were quadrantanopia of unknown reason, neovascular age-related macular degeneration, branch retinal vein occlusion, central retinal vein occlusion, macular vein occlusion, cystoid macular oedema, epiretinal membrane, lamellar macular hole and central serous retinopathy.

625 eyes of 374 patients met the inclusion criteria. In 251 patients both eyes met the inclusion criteria. To characterise VF progression rate and VF damage for an individual patient two definitions were applied: Definition A. Analysis of the eye with the greatest VF loss, Definition B. Analysis of the eye with the most rapid progression rate. In 168 of the 251 patients the same eye met the inclusion criteria for both definitions. In 83 patients the right eye met the criteria of one definition and the left eye the criteria of the other definition.

Statistical analysis

Descriptive statistics were used to analyse age, gender, number of VF, follow up time, baseline MD, final MD, progression rate in MD (dB/y) and in VFI (%/y), IOP mean in the 58 months period, IOP maximum, number of IOP readings, IOP standard deviation as a proxy for IOP fluctuation (as used in the Advanced Glaucoma Intervention Study (AGIS)[15]), treatment classes of ocular hypotensives, number of medical treatments and surgeries patients had had in the last 5 years. Stata statistics software version 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) was used for the scatter plots and the Pearson's correlation coefficients to assess the relationship between progression rate in MD (dB/y) and progression rate in VFI (%/y).

The simple linear regression models were used to study the relationships between progression rate in MD (dB/y) and factors presumably associated with progression (age, gender, baseline MD, CCT, glaucoma surgery, cataract surgery, mean IOP, IOP fluctuation, maximal IOP and type of treatment class). The potential predictors with a $p < 0.2$ according to the simple linear regression models were included in the multiple regression models with 1000 bootstrap samples. We applied the univariate and multivariable logistic regression models to evaluate the associations between fast progression (< -1 dB/y) and the same variables were used as in the linear regression model, except parasymapthomimetics. We used the Fisher's exact test for both definitions to assess an association between parasympathomimetics and fast

progression. The predictors with a p < 0.2 obtained from univariate models were used in the multivariable logistic regression models. The results were presented as odds ratio (OR) with 95% confidence intervals (CI). The goodness of model fitting was examined with the Hosmer-Lemeshow test. The data analysis was carried out using Stata statistics software version 14.2. The level of statistical significance was set at $p < 0.05$ with two tails.

Results

The mean age of the 374 patients who met the inclusion criteria was 69.5 years (standard deviation, SD: ± 9.06; median age: 71.5 years; interquartile range, IQR: 66.0–75.75 years). 47.9% of patients were women. The mean follow-up time was 3.5 years (SD ± 0.8) using both definitions for worse eyes. The mean progression rates were – 0.50 dB/y, -1.34 %/y (Definition A) and – 0.64 dB/y, -1.59 %/y (Definition B).

Table 1
Characteristics of patients sampled using both definitions (A) and (B)

Characteristics	(A) Greatest visual field loss Patients (n = 374)	(B) Most rapid progression rate Patients (n = 374)
Age, mean (SD), median (IQR)	69.51 (9.06); 71.5 (66.0-75.75)	69.51 (9.06); 71.5 (66.0-75.75)
Women, number (%)	179 (47.86%)	179 (47.86%)
Men, number (%)	195 (52.14%)	195 (52.14%)
Years of follow up, mean (SD)	3.47 (0.83)	3.47 (0.83)
Number of VF, mean ± SD	6.56 ± 1.44	6.58 ± 1.45
MD baseline (dB), mean ± SD; median (IQR)	-8.36 ± 6.54; -6.35 (-12.64 to -3.15)	-6.77 ± 5.91; -4.92 (-10.15 to -2.35)
MD final (dB), mean ± SD; median (IQR)	-9.48 ± 6.71; -7.84 (-14.19 to -3.99)	-8.21 ± 6.27; -6.63 (-11.66 to -3.21)
VFI baseline, mean ± SD, %	76.49 ± 19.58	81.55 ± 17.16
VFI final, mean ± SD, %	72.98 ± 20.64	77.25 ± 19.33
MD progression rate (dB/y), mean ± SD; median (IQR)	-0.50 ± 0.79; -0.40; (-0.80 to -0.10)	-0.64 ± 0.83; -0.50 (-0.90 to -0.1)
VFI progression rate, mean ± SD; median (IQR) (%/y)	-1.34 ± 2.60; -0.80 (-2.20 to 0)	-1.59 ± 2.58; -1.00 (-2.4 to -0.1)
IOP (mmHg), mean ± SD	14.88 ± 3.05	15.01 ± 2.99
IOP fluctuation (mmHg), mean ± SD	3.22 ± 1.94	3.20 ± 1.91
IOP maximum (mmHg), mean ± SD	21.19 ± 7.04	21.25 ± 6.95
Number of IOP readings, mean ± SD	11.68 ± 5.78	11.69 ± 5.79
CCT (μm), mean ± SD	548.13 ± 36.93	547.60 ± 36.98
Number of treatment classes, mean ± SD	2.24 ± 1.11	2.25 ± 1.08
0 treatment class, number (%)	34 (9.09%)	29 (7.75%)
1 treatment class, number (%)	54 (14.44%)	57 (15.24%)

† It was not considered when patients had undergone Selective Laser Trabeculoplasty (SLT) on two or three occasions. If both SLT and tube-shunt surgery or trabeculectomy had occurred, the incisional procedure was taken into account in the analysis.

Characteristics	(A) Greatest visual field loss Patients (n = 374)	(B) Most rapid progression rate Patients (n = 374)
2 treatment classes, number (%)	115(30.75%)	118 (31.55%)
3 treatment classes, number (%)	132 (35.29%)	131 (35.03%)
4 treatment classes, number (%)	39 (10.43%)	39 (10.43%)
5 treatment classes, number (%)	0 (0.00%)	0 (0.00%)
Prostaglandins, number (%)	320 (85.56%)	324 (86.63%)
Beta blockers, number (%)	252 (67.38%)	253 (67.65%)
Topical carbonic anhdrase inhibitors, number (%)	202 (54.01%)	202 (54.01%)
Alpha agonists, number (%)	60 (16.04%)	61 (16.31%)
Parasympathomimetics, number (%)	2 (0.53%)	2 (0.53%)
SLT, number (%) †	90 (24.06%)	90 (24.06%)
Trabeculectomy, number (%)	49 (13.10%)	52 (13.90%)
Tube shunt, number (%)	8 (2.14%)	7 (1.87%)
Cataract surgery, number (%)	53 (14.17%)	46 (12.30%)
† It was not considered when patients had undergone Selective Laser Trabeculoplasty (SLT) on two or three occasions. If both SLT and tube-shunt surgery or trabeculectomy had occurred, the incisional procedure was taken into account in the analysis.		

75.7% of eyes (A) and 80.8% of eyes (B) had negative MD slopes in the 58 months period. 19.0% (A) and 21.9% (B), 71 (A) and 82 (B) eyes were 'fast progressors' ($< -1dB/y$).

Table 2
Distribution of progression rates (decibels/year; dB/y)

Definition A	≥ -1 dB/y	between − 1 to -4 dB/y	≤ -4 dB/y	total
A	303	68	3	374
% of eyes A	81.02%	18.18%	0.80%	100%
B	292	77	5	374
% of eyes B	78.07%	20.59%	1.34%	100%

Distribution of progression rates in dB/y

A high positive linear correlation between the progression rate in VFI (%/y) and the progression rate in MD (dB/y), (Pearson's correlation coefficient r = 0.85; p < 0.001) (A), (r = 0.80; p < 0.001) (B) was observed.

The highest percentage of 'fast progressors' (< -1 dB/y) was found in the group with the baseline MD of -8 dB ≥ MD > -12 dB, when considering the eyes with the greatest visual field loss (A). In contrast, regarding the final MD, the highest percentage of 'fast progressors' was in the MD range between − 12 dB > MD ≥ -16 dB. In the eyes with the most rapid progression rate (B), the highest percentage of fast progressors was found in the same range of baseline and final MD between − 12 dB > MD ≥ -16 dB.

Table 3
'Fast progressors' baseline and final MD range in eyes with greatest visual field loss (Definition A) and in eyes with most rapid progression rate (Definition B)

(Definition) VF MD	>-4 (dB)	≤-4(dB)	≤-8(dB)	<-12(dB)	≤-16(dB)	≤-20(dB)
(A) Baseline total	122	91	60	45	33	23
(A) Baseline <-1 dB/y	20	18	16	10	6	1
(A) Baseline%<-1 dB/y	16.3%	19.78%	26.67%	22.22%	18.18%	4.35%
(A) Final total	94	94	65	51	37	33
(A) Final <-1dB/y	4	17	14	19	9	8
(A) Final%<-1 dB/y	4.26%	18.09%	21.54%	37.25%	24.32%	24.24%
(B) Baseline total	158	93	54	32	25	12
(B) Baseline<-1 dB/y	30	19	16	10	7	0
(B) Baseline%<-1 dB/y	18.99%	20.43%	29.63%	31.25%	28.00%	0.00%
(B) Final total	113	109	61	38	29	24
(B) Final <-1dB/y	7	22	17	18	10	8
(B) Final%<-1 dB/y	6.19%	20.18%	27.87%	47.37%	34.48%	33.33%

Gene therapy inclusion criteria

Using Definition A

When applying the gene therapy inclusion criteria (progression rate between − 1 to -4 dB/y; -4 dB ≥ MD ≥ -12 dB, ≤ -20 dB; age ≥ 50 years) on the eyes with the greatest visual field loss, Definition A, the following were observed. Thirty-one 'fast progressor' patients were in the MD range of -4 dB ≥ MD ≥ -12 dB. However, 1 was younger than 50 years, so 30 patients met the inclusion criteria. There were eight patients with a MD ≤ -20 dB, however, 1 patient progressed too rapidly at -4.2 dB/y, so 7 patients met the inclusion criteria. When considering both MD ranges applicable, 37 met the inclusion criteria for the gene therapy trial.

Using Definition B

In the eyes with the most rapid progression rate, Definition B, the following were observed. Thirty-nine patients were in the range of final MD of -4 dB ≥ MD ≥ -12 dB. One had a MD slope of -6.0 dB/y which was too rapid and 2 were too young to meet the inclusion criteria, leading to 36 eyes that met the inclusion criteria for the gene therapy trial. Eight 'fast progressors' were in the final MD range ≤ -20 dB, but one deteriorated at a rate of -4.2 dB/y. Therefore 7 met the inclusion criteria. In total, 43 patients met the inclusion criteria in the two MD ranges applicable for the gene therapy trial.

Factors associated with progression and fast progression

To identify potential covariates, the factors associated with progression and fast progression were assessed. Factors significantly associated with progression ($p < 0.05$) in the simple linear regression analysis of both definitions were age, prostaglandins, beta blockers and alpha agonists. In eyes defined by most rapid progression rate carbonic anhydrase inhibitors (the unstandardized coefficient (Beta/slope) (95%CI): -0.23 (-0.40, -0.07); $p = 0.005$) (Definition B) were also significantly negatively associated with progression. Parasympathomimetics (Beta coefficient (95%CI): 0.24 (0.07–0.41); $p = 0.006$) (Definition B) were significantly positively associated with the progression rate.

The factors at $p < 0.2$ were included in the multiple linear regression analysis. Age ($p = 0.014$) (Definition A), ($p = 0.006$) (Definition B), prostaglandins ($p = 0.008$) (Definition A), ($p = 0.001$) (Definition B) and alpha-agonists ($p = 0.002$) (Definition A), ($p = 0.005$) (Definition B) were significantly associated with progression in the multiple linear regression model. In eyes with most rapid progression rates, parasympathomimetics remained significantly positively associated ($p < 0.001$) (Definition B) with progression rates in the multiple linear regression analysis.

Table 5
Linear regression analysis of eyes with greatest visual field loss (Definition A)

Factor	Simple linear regression			Multiple linear regression ♯		
	Beta	(95%CI)	p value	Beta	(95%CI)	p value
Age (years)	-0.01	(-0.02, -0.002)	0.02	-0.01	(-0.02, -0.002)	0.014
Male	-0.004	(-0.17, 0.16)	0.96			
Baseline MD	-0.01	(-0.02, 0.01)	0.33			
Pachymetry	-0.001	(-0.003, 0.001)	0.52			
Glaucoma surgery (ref)			0.65			
SLT	0.01	(-0.18, 0.21)	0.91			
Trabeculectomy	-0.17	(-0.44, 0.10)	0.22			
Tube-Shunt	-0.03	(-0.79, 0.74)	0.94			
Cataract surgery	-0.15	(-0.41, 0.12)	0.28			
Prostaglandins	-0.27	(-0.42, -0.11)	0.001	-0.21	(-0.37, -0.06)	0.008
Beta blockers	-0.17	(-0.32, -0.02)	0.04			
Carbonic anhydrase Inhibitors	-0.13	(-0.28, 0.03)	0.11			
Alpha agonists	-0.46	(-0.74, -0.17)	0.001	-0.43	(-0.71, -0.15)	0.002
Parasympatho-mimetics	0.11	(-0.07, 0.28)	0.24			
IOP mean		(-0.01, 0.03)	0.48			
IOP fluctuation	-0.76	(-0.06, 0.04)	0.65			
IOP maximum		(-0.02, 0.01)	0.72			
♯Adj R-squared = 0.07						

In the univariate logistic regression analysis, prostaglandins, beta blockers and alpha agonists were risk factors ($p < 0.05$) for fast progression (< -1 dB/y). Carbonic anhydrase inhibitors (OR (95%CI): 1.88 (1.23–3.23); $p = 0.016$) (Definition B) were also significantly associated with fast progression in the univariate model of eyes with most rapid progression rate. All factors at a $p < 0.2$ were included in the multivariable model, except prostaglandins, since the 95% CI of OR was very wide (using definitions A and B).

In the multivariable logistic regression model, beta blockers (OR (95%CI): 2.84 (1.39–5.80); $p = 0.004$) (Definition A), (OR (95%CI): 2.48 (1.30–4.75); $p = 0.006$) (Definition B) and alpha agonists (OR (95%CI):

2.18 (1.14–4.17); p = 0.02) (Definition A), (OR (95%CI): 2.00 (1.08–3.73); p = 0.028) (Definition B) were associated with fast progression of the VF in both definitions of worst eyes. Gender was borderline significant (OR (95%CI): 0.60 (0.36-1.00); p = 0.05) (Definition B) in eyes with most rapid progression rate. The Hosmer and Lemeshow's goodness-of-fit test indicated that the model fitted the data well (p = 0.27) (Definition A) and satisfactorily (p = 0.051) (Definition B). The Fisher's exact test was performed for parasympathomimetics (p = 1.00) (Definitions A and B).

Table 6
Linear regression analysis of eyes with most rapid progression rate (Definition B)

Factor	Simple linear regression			Multiple linear regression §		
	Beta	(95%CI)	p value	Beta	(95%CI)	p value
Age (years)	-0.01	(-0.03, -0.004)	0.007	-0.01	(-0.02, -0.004)	0.006
Male	0.01	(-0.15, 0.18)	0.88			
Baseline MD	0.01	(-0.01, 0.02)	0.41			
Pachymetry	-0.0004	(-0.003, 0.002)	0.72			
Glaucoma surgery (ref)			0.45			
SLT	0.01	(-0.17, 0.20)	0.88			
Trabeculectomy	-0.20	(-0.48, 0.07)	0.14			
Tube-shunt	-0.13	(-0.98, 0.72)	0.76			
Cataract surgery	-0.05	(-0.33, 0.22)	0.70			
Prostaglandins	-0.35	(-0.51, -0.18)	< 0.001	-0.25	(-0.41, -0.10)	0.001
Beta blockers	-0.24	(-0.40, -0.08)	0.004			
Carbonic anhydrase Inhibitors	-0.23	(-0.40, -0.07)	0.005			
Alpha agonists	-0.44	(-0.70, -0.19)	0.001	-0.38	(-0.65, -0.12)	0.005
Parasympatho-mimetics	0.24	(0.07, 0.41)	0.006	0.27	(0.13, 0.42)	< 0.001
IOP mean	0.01	(-0.01, 0.04)	0.37			
IOP fluctuation	-0.01	(-0.06, 0.04)	0.72			
IOP maximum	-0.001	(-0.02, 0.01)	0.92			
§ Adj R-squared = 0.08.						

Table 7
Results of the univariate and multivariable logistic regression analysis of eyes defined by greatest visual field loss (Definition A)

Factor	Univariate model		Multivariable model	
	OR (95%CI)	p value	OR (95%CI)	p value
Age (years)	1.02 (0.99–1.05)	0.31		
Male	0.70 (0.42–1.18)	0.19		
Baseline MD	1.01 (0.97–1.05)	0.72		
Pachymetry	1.00 (0.99–1.01)	0.24		
Glaucoma surgery (ref)		0.53		
SLT	0.98 (0.52–1.86)	0.95		
Trabeculectomy	1.64 (0.80–3.36)	0.18		
Tube-shunt	0.64 (0.08–5.41)	0.69		
Cataract surgery	1.66 (0.85–3.26)	0.14		
Prostaglandins	7.15 (1.70-30.08)	0.007		
Beta blockers	3.15 (1.59–6.25)	0.001	2.84 (1.39–5.80)	0.004
Carbonic anhydrase Inhibitors	1.61 (0.94–2.74)	0.08		
Alpha agonists	2.58 (1.39–4.77)	0.003	2.18 (1.14–4.17)	0.02
IOP mean	0.99 (0.91–1.08)	0.91		
IOP fluctuation	1.01 (0.89–1.16)	0.21		
IOP maximum	1.01 (0.97–1.05)	0.59		

Table 8
Results of the univariate and multivariable logistic regression analysis of eyes defined by most rapid progression rate (Definition B)

Factor	Univariate model		Multivariable model	
	OR (95%CI)	p value	OR (95%CI)	p value
Age (years)	1.02 (0.99–1.05)	0.26		
Male	0.70 (0.43–1.14)	0.15	0.60 (0.36-1.0)	0.05
Baseline MD	0.98 (0.94–1.02)	0.30		
Pachymetry	1.00 (0.99–1.01)	0.46		
Glaucoma surgery (ref)		0.53		
SLT	0.91 (0.49–1.68)	0.76		
Trabeculectomy	1.89 (0.97–3.67)	0.06		
Tube-shunt	1.56 (0.29–8.28)	0.60		
Cataract surgery	1.48 (0.74–2.96)	0.27		
Prostaglandins	7.87 (1.87–33.11)	0.005		
Beta blockers	2.81 (1.51–5.24)	0.001	2.48 (1.30–4.75)	0.006
Carbonic anhydrase Inhibitors	1.88 (1.23–3.23)	0.016		
Alpha agonists	2.38 (1.31–4.31)	0.004	2.00 (1.08–3.73)	0.028
IOP mean	0.99 (0.92–1.09)	0.99		
IOP fluctuation	1.06 (0.94–1.19)	0.37		
IOP maximum	1.02 (0.98–1.05)	0.33		

Discussion

As the Cambridge University Hospital Glaucoma Clinic receives tertiary referrals, the patients treated at the hospital are more likely to suffer from severe and recalcitrant glaucoma. Therefore, the analysis of POAG patients at the Cambridge University glaucoma clinic represents an enriched source of patients that may be suitable for a gene therapy trial.

Two definitions were applied to characterise visual field progression rate using Guided Progression Analysis as a gene therapy trial would include one eye per patient and both definitions are eligible for defining the worst eye per patient. Definition A, taking the eye with the greatest visual field loss into account, would make the progression rates comparable to a study involving Swedish patients.[4] Definition B, choosing the eye with the most rapid progression rate in the period evaluated, could

potentially be advantageous to the patient in that this eye would have a more immediate effect if the gene therapy were effective in slowing the progression rate. Interestingly, a higher number of eyes were eligible for the gene therapy trial when considering the eyes with the most rapid progression rates (Definition B).

Compared to other studies, the period evaluated (58 months) and the resulting mean follow up time (3.47 years) was relatively small.[13, 4, 2] This was unavoidable as the Epic Systems software was implemented in October 2014 at Cambridge University Hospitals. Yet all information concerning treatments, medication and diagnosis was available due to the comprehensive nature of this electronic medical record. However, with only including patients, who had at least 5 VF in these 58 months, it was assured that there were enough VF to assess the progression rate.[4, 7] As a major change in the visual fields was unlikely to occur in 1 or 2 years, we deemed that patients had to have at least a 3 years series of visual fields, as in the study by Saunders et al.[8] GPA was used to calculate the progression rates per year, a method also used by the United Kingdom Glaucoma Treatment Study (UKGTS) to quantify VF progression.[16] To reduce the risk that the progression rates might be biased by the learning effect between the first ever done and second VF, the first ever done VF was excluded.[17]

The retrospective study design could be a potential weakness, as progression rates might be higher when looking at patients retrospectively, rather than monitoring them under a randomized controlled trial setting. In a randomized controlled trial setting, patients are monitored in certain time intervals and ophthalmologists can react to more rapid progression rates by adjusting the treatment. A strength of the retrospective design may be that these progression rates may give a more pragmatic reflection of rates seen in a normal clinical environment.

Progression rates in comparison to other studies

The progression rates of the Cambridge patient cohort, with a mean rate of -0.50 dB/y (Definition A) and – 0.64 dB/y (Definition B) were lower than the rates of change reported by Heijl et al.[8] An explanation for the higher progression rates in Sweden might be the fact that the study in Sweden also included patients with Pseudoexfoliation glaucoma.[4] The progression rates at Cambridge University Hospital were comparable to the rates of deterioration of -0.48 dB/y which were reported, when POAG patients of the GAPS were analysed.[9] The median progression rates at Addenbrooke's Hospital were also higher than those reported by other British studies. The median progression rate of -0.15 dB/y was reported in the worst eye of patients with glaucomatous damage in a study by Saunders et al.[8] Kirwan et al[7] reported a median progression rate of -0.1 dB/y when analysing the better eye per patient of ocular hypertension and glaucoma patients. It must be considered that these two studies did not specifically analyse patients with the diagnosis POAG.[8, 7] The mean progression rates of patients under standard clinical care in Canada were – 0.15 dB/y.[6] Additionally, the CGS, with the median age of patients being 65.2 years, reported median progression rates of -0.35 dB/y in progressing eyes.[5] The older age of the Cambridge patients (71.5 years was the median age) and the fact that the clinics consist of more severe glaucoma

cases (less severe cases are often seen in off-site shared care glaucoma clinics operated by optometrists but supervised by ophthalmologists) may be the reason for the higher progression rates we observed.

Feasibility of the gene therapy inclusion criteria

19.0% (Definition A) and 21.9% (Definition B), approximately 1 out of 5 patients deteriorated < -1 dB/y, despite standard treatment. 37 (Definition A) and 43 (Definition B) of the 71 (Definition A) and 82 (Definition B) eyes, which progressed at rates < -1 dB/y, met the putative gene therapy inclusion criteria. Based on the criteria for gene therapy concerning the progression rate (progression rate between − 1 and − 4 dB/y), 1 (Definition A) and 2 (Definition B) patients in the final MD range applicable for the gene therapy trial progressed at a too high progression rate. When not taking the MD range for the gene therapy trial into account, 3 (Definition A) and 5 (Definition B) patients were progressing above − 4 dB/y. In total, 14 patients were younger than 50 years of age, of whom 4 (Definition A) and 5 (Definition B) were 'fast progressors'. When all other criteria (-4 dB ≥ MD ≥ -12 dB; ≤ -20 dB; progression rate between − 1 and − 4 dB/y) for a gene therapy trial were applied, the age cut-off of 50 excluded 1 patient (Definition A) and 2 patients (Definition B). However, as the prevalence of POAG rises with age, the threshold of 50 years is probably a reasonable threshold to use.[18] Due to the fact that the gene therapy trial would only include eyes in the MD range between − 4 dB ≥ MD ≥ -12 dB and ≤ -20 dB, 32 (Definition A) and 35 (Definition B) 'fast progressor' patients were excluded, since they did not meet this inclusion criterion. Just 4 (Definition A) and 7 (Definition B) 'fast progressors' had a MD > -4 dB, indicating that the threshold of including patients with a MD ≤ -4 dB is realistic.

Covariates that may have implications for a gene therapy trial

In the analysis of the Cambridge patients, a significant factor for progression was age, as it was also shown in Sweden, in the CGS and in the AGIS.[13, 4, 12] In the logistic regression analysis for factors associated with fast progression, male gender reached borderline significance in being protective of visual field deterioration in eyes defined by most rapid progression rate (Definition A). This result is different to the analysis of patients of the GAPS, where male gender was associated with a higher risk of progression in those with lower intraocular pressure.[2] However, in the CGS female gender imposed a greater risk of deterioration with a hazard ratio of 1.94.[13]

In contrast to other studies, IOP parameters were neither associated with progression nor with fast progression in our POAG patients.[13, 4, 12, 2] In comparison to the Cambridge patient cohort, the mean IOP was higher in Sweden where 20.15 mmHg was measured at the beginning of the study period decreasing by 2.05 mmHg at the end.[4] In the Cambridge cohort the mean follow up IOP was 14.88 mmHg (Definition A) and 15.01 mmHg (Definition B).

Notably, the mean central corneal thickness with 548.13 µm (SD ± 36.93) (Definition A) and 547.60 µm (SD ± 36.98) (Definition B) was very similar to average CCT (mean, 547 µm; SD, ± 41) in the Canadian study which reported no correlation between CCT and glaucomatous visual field progression.[19] CCT

was a significant risk factor for progression in the GAPS where mean CCT was thinner (mean, 540.9 μm; SD, ± 37.3).[2]

In the study by Heijl et al[4], laser treatment and trabeculectomy were both associated with more negative rates of change. However, the covariate for glaucoma surgery that included SLT, tube-shunt surgery and trabeculectomy, neither correlated significantly with progression nor with fast progression in the Cambridge cohort. The difference between these studies in relation to the effect of operative interventions on progression rate may be explained by the much longer duration of follow-up in the Swedish study (5 years between March 1996 to August 2005) or differences in frequency of laser and interventional surgeries used (more patients in the Swedish study underwent laser, 31% compared to 24%, but fewer had trabeculectomies, 10% versus 13%).[4]

Baseline MD was neither significantly associated with progression nor fast progression in the Cambridge cohort as was also reported by the GAPS.[3] This finding was also reported by another study by de Moraes et al.[2] These results are in contrast to the Swedish study, where a significant relationship between initial MD and progression rate was reported.[4] Importantly however, the median baseline MD of the Cambridge patients, with − 6.35 dB (Definition A) and − 4.92 dB (Definition B), was better than the median baseline MD of -10 dB, which was reported by the Swedish study. [4]

The finding that patients on certain medication classes progressed at higher rates, may of course arise from the fact that patients who progressed were prescribed more medication classes and beta blockers and alpha agonists were more likely to be additionally prescribed in 'fast progressors'. Alpha agonists and prostaglandins (using both progression definitions) were also significantly correlated with more negative MD slopes.

Conclusion

To our knowledge, this is the first time that factors associated with fast progression defined by the MD slope < -1 dB/y have been analysed. Our analysis of demographic factors would not usefully assist a clinician in determining which patient will progress fast or more slowly, nor were there factors associated with the types of treatment offered which could be predictive covariates in the selection of potential patients for a gene therapy trial. More important however was the finding that the inclusion criteria for a POAG gene therapy trial would apply to at least half (52%) of the 'fast progressor' patients in this glaucoma clinic population.

Declarations

Acknowledgment

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References

1. Bourne RR, Stevens GA, White RA, Smith JL, Flaxman SR, Price H, Jonas JB, Keeffe J, Leasher J, Naidoo K, Pesudovs K, Resnikoff S, Taylor HR (2013) Causes of vision loss worldwide, 1990-2010: a systematic analysis. Lancet Glob Health 1 (6):e339-349. doi:10.1016/s2214-109x(13)70113-x

2. De Moraes CG, Juthani VJ, Liebmann JM, Teng CC, Tello C, Susanna R, Jr., Ritch R (2011) Risk factors for visual field progression in treated glaucoma. Arch Ophthalmol 129 (5):562-568. doi:10.1001/archophthalmol.2011.72

3. Forchheimer I, de Moraes CG, Teng CC, Folgar F, Tello C, Ritch R, Liebmann JM (2011) Baseline mean deviation and rates of visual field change in treated glaucoma patients. Eye (Lond) 25 (5):626-632. doi:10.1038/eye.2011.33

4. Heijl A, Buchholz P, Norrgren G, Bengtsson B (2013) Rates of visual field progression in clinical glaucoma care. Acta Ophthalmol 91 (5):406-412. doi:10.1111/j.1755-3768.2012.02492.x

5. Chauhan BC, Mikelberg FS, Artes PH, Balazsi AG, LeBlanc RP, Lesk MR, Nicolela MT, Trope GE (2010) Canadian Glaucoma Study: 3. Impact of risk factors and intraocular pressure reduction on the rates of visual field change. Arch Ophthalmol 128 (10):1249-1255. doi:10.1001/archophthalmol.2010.196

6. Chauhan BC, Malik R, Shuba LM, Rafuse PE, Nicolela MT, Artes PH (2014) Rates of glaucomatous visual field change in a large clinical population. Invest Ophthalmol Vis Sci 55 (7):4135-4143. doi:10.1167/iovs.14-14643

7. Kirwan JF, Hustler A, Bobat H, Toms L, Crabb DP, McNaught AI (2014) Portsmouth visual field database: an audit of glaucoma progression. Eye (Lond) 28 (8):974-979. doi:10.1038/eye.2013.294

8. Saunders LJ, Russell RA, Kirwan JF, McNaught AI, Crabb DP (2014) Examining Visual Field Loss in Patients in Glaucoma Clinics During Their Predicted Remaining LifetimePredicted Lifetime Visual Field Loss in Glaucoma. Investigative Ophthalmology & Visual Science 55 (1):102-109. doi:10.1167/iovs.13-13006

9. De Moraes CG, Liebmann JM, Liebmann CA, Susanna R, Jr., Tello C, Ritch R (2013) Visual field progression outcomes in glaucoma subtypes. Acta Ophthalmol 91 (3):288-293. doi:10.1111/j.1755-3768.2011.02260.x

10. Waisbourd M, Ahmed OM, Molineaux J, Gonzalez A, Spaeth GL, Katz LJ (2016) Reversible structural and functional changes after intraocular pressure reduction in patients with glaucoma. Graefe's Archive for Clinical and Experimental Ophthalmology 254 (6):1159-1166. doi:10.1007/s00417-016-3321-2

11. Osborne A, Khatib TZ, Songra L, Barber AC, Hall K, Kong GYX, Widdowson PS, Martin KR (2018) Neuroprotection of retinal ganglion cells by a novel gene therapy construct that achieves sustained enhancement of brain-derived neurotrophic factor/tropomyosin-related kinase receptor-B signaling. Cell Death Dis 9 (10):1007. doi:10.1038/s41419-018-1041-8

12. Nouri-Mahdavi K, Hoffman D, Coleman AL, Liu G, Li G, Gaasterland D, Caprioli J (2004) Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. Ophthalmology 111 (9):1627-1635. doi:10.1016/j.ophtha.2004.02.017

13. Chauhan BC, Mikelberg FS, Balaszi AG, LeBlanc RP, Lesk MR, Trope GE (2008) Canadian Glaucoma Study: 2. risk factors for the progression of open-angle glaucoma. Arch Ophthalmol 126 (8):1030-1036. doi:10.1001/archopht.126.8.1030

14. De Moraes CG, Prata TS, Tello C, Ritch R, Liebmann JM (2009) Glaucoma with early visual field loss affecting both hemifields and the risk of disease progression. Arch Ophthalmol 127 (9):1129-1134. doi:10.1001/archophthalmol.2009.165

15. Ederer F, Gaasterland DE, Sullivan EK (1994) The Advanced Glaucoma Intervention Study (AGIS): 1. Study design and methods and baseline characteristics of study patients. Control Clin Trials 15 (4):299-325

16. Garway-Heath DF, Lascaratos G, Bunce C, Crabb DP, Russell RA, Shah A (2013) The United Kingdom Glaucoma Treatment Study: a multicenter, randomized, placebo-controlled clinical trial: design and methodology. Ophthalmology 120 (1):68-76. doi:10.1016/j.ophtha.2012.07.028

17. Heijl A, Bengtsson B (1996) The effect of perimetric experience in patients with glaucoma. Arch Ophthalmol 114 (1):19-22. doi:10.1001/archopht.1996.01100130017003

18. Weih LM, Nanjan M, McCarty CA, Taylor HR (2001) Prevalence and predictors of open-angle glaucoma: Results from the visual impairment project. Ophthalmology 108 (11):1966-1972. doi:https://doi.org/10.1016/S0161-6420(01)00799-0

19. Chauhan BC, Hutchison DM, LeBlanc RP, Artes PH, Nicolela MT (2005) Central corneal thickness and progression of the visual field and optic disc in glaucoma. The British journal of ophthalmology 89 (8):1008-1012. doi:10.1136/bjo.2004.062927

Figures

Image not available with this version

Figure 1

Definition A. Progression rate in MD (dB/y) and progression rate in VFI (%/y). Stata statistics software version 14.2 was used.

Image not available with this version

Figure 2

Definition B. Progression rate in MD (dB/y) and progression rate in VFI (%/y). Stata statistics software version 14.2 was used.