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The glaucoma intensive treatment study: interim results from an ongoing longitudinal randomized clinical trial

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ABSTRACT.

Purpose: **The aim of the study was to determine the perimetric rate of glaucoma progression in the ongoing Glaucoma Intensive Treatment Study (GITS) after 3 years of follow-up.**

Design: **This is a randomized, two-centre, prospective open-labelled treatment trial for open-angle glaucoma (OAG).**

Participants: **The participants of this study were treatment-naive patients with newly diagnosed OAG, aged 46–78 years, with early to moderate glaucomatous visual field loss scheduled to be followed for 5 years within the study.**

Methods: **Patients were randomized to initial treatment with either topical monotherapy or with an intensive approach using drugs from three different classes, plus 360° laser trabeculoplasty. Changes in treatment were allowed. Standard automated perimetry and tonometry were performed and side-effects documented. All results are presented using intention-to-treat analysis.**

Results: **A total of 242 patients were randomized. After 3 years of follow-up, eight patients were lost to follow-up, six of whom were deceased. The median untreated baseline intraocular pressure (IOP) was 24 mmHg in both arms. The median IOP was almost constant over the 3 years of follow-up: ≈17 mmHg in the mono-arm and ≈14 mmHg in the multi-treatment arm. Treatment was intensified in 42% of the mono-treated patients and in 7% of the multi-treated patients. Treatment was reduced in 13% of the multi-treated patients. The median perimetric rate of progression was −0.5%/year in the mono-treated group and −0.1%/year in the multi-treated group (p = 0.03).**

Conclusion: **The rate of disease progression was significantly slower in the multi-treated patients than in the mono-treated patients. Further follow-up will show whether this difference is sustained over time.**

Key words: drug trial – glaucoma – progression – RCT – visual field

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Introduction

Randomized clinical trials comparing medical treatment with no treatment or with placebo have provided evidence of the benefit of intraocular pressure (IOP)-lowering treatment on the course of visual field loss in open-angle glaucoma (OAG) (Collaborative Normal-Tension Glaucoma Study Group 1998; Heijl et al. 2002; Garway-Heath et al. 2015). A number of trials have compared the effects different types of IOP-lowering drugs, laser treatment and surgery, on visual field development in glaucomatous eyes (Migdal et al. 1994; AGIS Investigators 1998; Musch et al. 2009; Swaminathan et al. 2020; Wright et al. 2020).

The event of progression of the visual field defects and the time to the event of progression are often employed as primary outcomes in glaucoma treatment trials. The perimetric rate of progression is usually expressed as the slope of a linear regression of a summary index over time and may be a more important outcome because it quantifies the speed of progression and can be used to predict future field loss (McNaught et al. 1995; Crabb et al. 1997; Nouri-Mahdavi et al. 2004; Bengtsson et al. 2009; Medeiros et al. 2012; Bryan et al. 2013; Saunders et al. 2014). Ideally, treatment should halt the progression of glaucoma, but this is not a realistic goal. Glaucoma progression rates have been found to be highly variable among patients. A slow

progression rate in a patient with initial early damage and a short life expectancy is not likely to cause problems for that patient, whereas rapid progression in a patient with a longer life expectancy greatly increases the risk that the patient will suffer a reduction in vision-related quality of life (QoL) during his/her lifetime. Prediction of visual field loss by extrapolation of the slope to the estimated time point for the end of life, calculated as the residual life expectancy, can help us identify patients at risk of developing severe glaucomatous visual field loss (European Glaucoma Society's Guidelines 5th ed. 2020). More rapid rates of progression indicate the need for more aggressive treatment.

The European Glaucoma Society's Guidelines (5th ed. 2020) state that: 'The goal of care for people with, or at risk of, glaucoma is to promote their well-being and quality of life (QoL) within a sustainable healthcare system. Well-being and QoL are influenced by a person's visual function, the psychological impact of having a chronic progressive sight-threatening condition and the costs and side-effects of treatment'.

The conventionally recommended treatment regimen for IOP-lowering therapy is to set a target IOP and to start treatment with one type of drug and see if the target has been reached. If not it is customary to switch to another drug if the first was ineffective or add another drug if the first was effective, but the target still was not met. Once target IOP is reached, one will wait and see whether further reduction is needed based on disease development. This traditional stepwise increase in treatment may delay IOP reduction to sufficiently low levels in some glaucoma patients.

The Glaucoma Intensive Treatment Study (GITS) was initiated to compare initial intensive treatment using multiple drug therapy with eye drops containing a fixed combination of drugs from two different classes in one bottle, plus a single drug from a third class, followed by 360° laser trabeculoplasty (LTP), to conventional initial treatment with monotherapy, that is, starting with one IOP-lowering agent. To our knowledge, no previous studies compared the effect of the conventional approach of stepwise treatment escalation with an initial intensive noninvasive approach on glaucomatous visual field development.

The purpose of this paper is to present interim results on the perimetric rate of progression in the two treatment arms of the GITS, that is, the standard stepwise regimen and more intensive initial treatment, and to report documented side-effects and adverse events (AEs) likely to be caused by the IOP-lowering treatment after three years of follow-up.

Methods

Glaucoma Intensive Treatment Study is an ongoing two-centre, prospective, open-labelled randomized controlled trial including patients with primary OAG and pseudoexfoliation glaucoma. The design and methodology of GITS have been described previously (Bengtsson et al. 2018). Briefly, patients aged between 40 and 78 years with newly diagnosed previously untreated OAG and a summary visual field index (VFI) implemented in the Humhprey Field Analyzer (HFA; Carl Zeiss Meditec, Dublin, CA, USA) better than, or equal to, 65% in the worse eye, were consecutively included in GITS. The reason for applying a lower limit for VFI was to avoid truncation of the rate of perimetric progression in glaucomatous eyes with high risk to progress to severe stages. Glaucoma was defined as repeatable visual field defects measured by standard automated perimetry with the HFA 30-2 SITA Standard program and a corresponding morphological glaucomatous change in the optic disc and/or the retinal nerve fibre layer. Patients with contraindications for glaucoma medications that would prevent multitherapy or any obstacle to LTP were not included. No upper or lower limits were applied to untreated IOP.

Ethics

Glaucoma Intensive Treatment Study adheres to the tenets of the Declaration of Helsinki and has been approved by the Regional Ethics Review Board in Lund, Sweden (Ref. no. 2013/697). Eligibility for inclusion was assessed at two prestudy visits before the baseline visit, and eligible subjects were given oral and written information. The included patients gave their oral and written informed consent to participate in the study. GITS has also been approved by the Swedish Medical Product Agency (Ref. no. 5.1-2013-64667) and is registered in EudraCT (Ref. no. 2013-002895-42).

Treatment

The patients were randomized at a 1:1 ratio to initially receive one of the two treatment regimens: mono-treatment or multi-treatment. One or both eyes were included in the study, depending on eligibility. Patients in whom both eyes were included were prescribed the same IOP-lowering mono- or multi-treatment for both eyes. In patients where only one eye was included, the fellow eye could be treated, if necessary. In the mono-treated group, the fellow eye was typically treated with the same drug as the study eye. In the multi-treated group, treated fellow eyes usually received one, or sometimes two, of the drugs administered to the study eye.

Patients randomized to mono-treatment were typically prescribed prostaglandin (81%) or a beta blocker (19%) but could be prescribed any type of monotherapy approved and registered for use in Sweden (Lindén et al. 2018). Patients randomized to multi-treatment were prescribed any type of fixed combination drops approved and registered for use in Sweden, plus a third agent from a third class of drugs. One week after the initiation of treatment with eye drops, 360° LTP was performed with selective laser trabeculoplasty (SLT) or argon laser trabeculoplasty (ALT).

Treatment could be changed or intensified, as necessary, at the discretion of the treating ophthalmologist and in consultation with the patient, when rapid progression was observed, if IOP reduction was considered insufficient, or when side-effects were observed. The treating ophthalmologists were all glaucoma specialists, three in Malmö (SAG, JA and AH) and two in Umeå (GH and CL). All staff involved in the study, ophthalmologists as well as technicians/nurses, were acquainted with the different procedures stipulated in the manual of operation and were certified for their roles in GITS. The same five ophthalmologists have been active in GITS from the start.

Patient visits

The GITS protocol stipulates a minimum number of visits. Patients were thus scheduled for five visits including

the baseline visit during the first year of follow-up and for a total of nine visits during the first three years of follow-up. Standard automated perimetry was performed at nine visits, once at each of the two prestudy visits and then at another seven visits during the first three years of follow-up. Additional visits occurred when deemed necessary.

Tests and measures

In this article, we focus on visual field progression, IOP, side-effects and any AE possibly or probably associated with the glaucoma medication and sufficiently important to be reported or cause a change in treatment. During the follow-up, the patient's visual field was assessed with the SITA Standard 24-2 program. Tests with >15% false-positive responses were considered unreliable and were, if possible, repeated after a short break during the same visit, or at an extra visit. Fixation was assessed by the built-in gaze tracker or by a visible blind spot on the grey scale map having a threshold value of <10 dB and by the perimetrist intermittently checking fixation on the screen during the examination.

The visual field index is a global index similar to the global mean deviation (MD) index but is expressed in percent of a full field. The VFI was developed to calculate the perimetric rate of progression but not to detect early visual field loss. The VFI is considerably less sensitive to developing cataracts and more heavily weighted towards the centre of the field than the MD index (Bengtsson & Heijl 2008). To avoid the effects of learning (Wild et al. 1989; Heijl & Bengtsson 1996), the rate of progression based on the VFI was calculated starting with the results obtained at the second prestudy visit, prior to the baseline visit. The rate of progression was calculated using Glaucoma Progression Analysis software implemented in the Humphrey Field Analyzer (Heijl et al. 2012). IOP was measured once at all follow-up visits using calibrated Goldmann applanation tonometers.

Patients were asked about side-effects and AEs at all scheduled visits, and AEs were also spontaneously reported by the patients.

All AEs were documented, except those that were mild and already registered in the National Reference Safety Information in the Summary of Product Characteristics as commonly known. Mild AEs are only reported in this article when they led to a change in therapy. A change to preservative-free eye drops containing the same active agents as a result of an adverse event was reported as an adverse effect causing a change in treatment.

Outcome measures

The primary outcome reported in this article is the perimetric rate of progression after 3 years of follow-up. The study protocol stipulates that the rate of progression is to be assessed after 3 and 5 years of follow-up. The secondary outcomes are IOP during the 3-year visits and the frequency of AE and Serious AE (SAE) assessed as possibly or probably associated with the treatment.

Analysis

Intention-to-treat analysis was employed. Thus, all patients, except two (three eyes) with no follow-up data, were analysed in the treatment group to which they were randomly assigned, using all data up to 3 years of follow-up or to the time of drop-out. One patient was found not to fulfil the eligibility criteria after randomization as the correct diagnosis was pigmentary glaucoma, but the data were included in the analysis according to the intention-to-treat principle.

The perimetric rate of progression requires at least five tests to be calculated by linear regression of the VFI over time and is expressed as the percentage of loss of the global field per year. The regression scatter plots for all the eyes included in the study were closely examined to identify obvious deviation from linearity, and no important deviation from linearity could be identified. The distribution of the rates of progression slopes was negatively skewed with a longer negative tail, which is in agreement with most reports on the rate of progression of visual field loss in glaucomatous eyes (Collaborative Normal-Tension Glaucoma Study Group 2001; Saunders et al. 2004; Heijl et.al. 2009; Heijl et al. 2013). Descriptive statistics are therefore presented as median and 95% confidence interval (CI) derived from the empirical distributions. In 50 patients, both eyes were eligible and subsequently included in the study. The other 184 patients contributed with one eye each. Because the distribution of rates of perimetric progression was skewed, in the current sample, the skewness was −7.4, we could not use the mixed model. We tried different transformations of the dependent variable, rate of perimetric progression, but could not find one resulting in a linear model. The generalized estimating equations model with gamma distribution can be used for skewed data, but only on positive values. Our data included both negative and postive values. Therefore, in patients having two eyes included, we calculated and used the mean rate of perimetric progression of the two eyes, resulting in one rate of progression value for each patient. Then we performed a nonparametric Mann–Whitney *U* test to compare the distributions of patients' rate of progression between the two treatment arms.

The baseline IOP, before treatment, was defined as the mean of three different values obtained on three separate visits, namely, the two prestudy visits and the baseline visit. The baseline and all follow-up distributions of IOP were positively skewed and therefore described in terms of median and empirically derived 95% CI. IBM SPSS version 25.0 IBM (New York, NY, USA) was used for data analysis.

The sample size calculation performed for the GITS (Bengtsson et al. 2018) was based on the perimetric rate of progression data from a large clinical study of all OAG patients in standard care who had been followed up at the Department of Ophthalmology at Malmö University Hospital in Sweden, which provides primary as well as tertiary care (Heijl et al. 2013). A p-value <0.05 was considered significant.

Results

Recruitment started in a pilot format in March 2013 to June 2013 and ended in March 2017. A total of 242 newly diagnosed glaucoma patients were included in GITS: 143 eyes in 118 patients were randomized to the mono-treatment arm and 155 eyes of 124 patients to the multi-treatment arm (for details, see Fig. 1). The median age in the mono-treated group was 68 years, and 69 years in the multi-

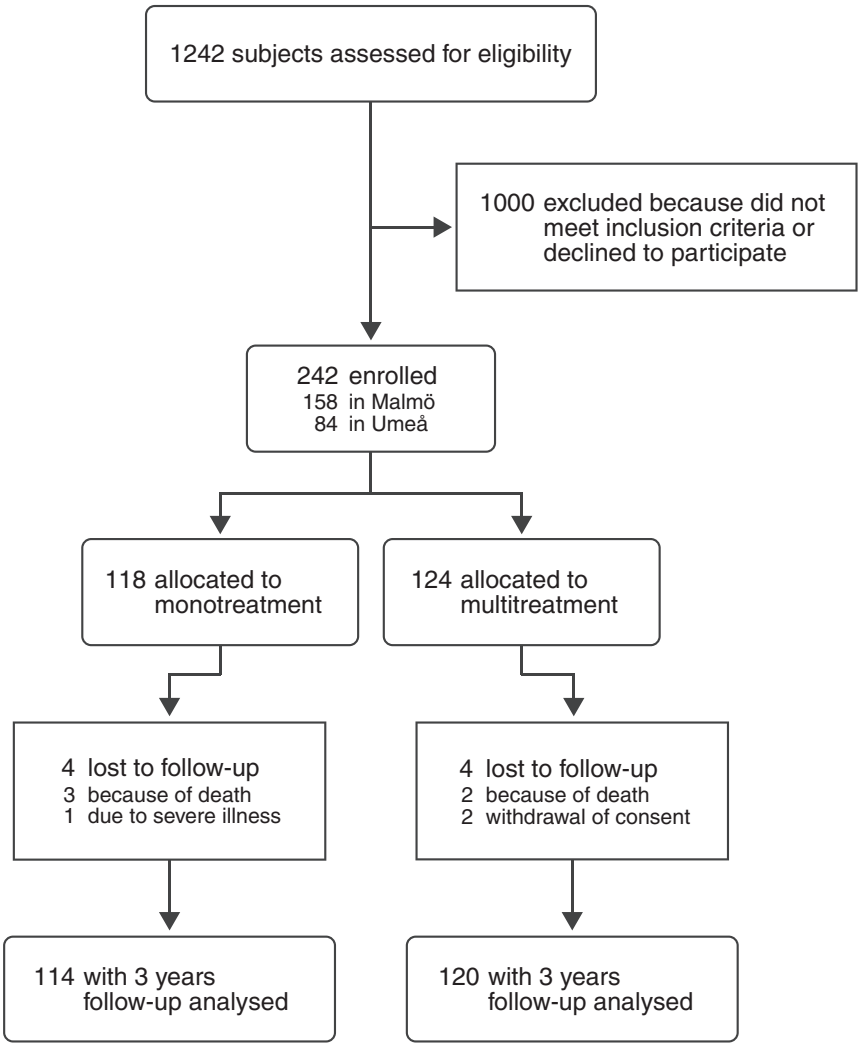

Fig. 1. Study profile. The vast majority of subjects assessed for eligibility was excluded. We were very generous in examining all new patients and referrals to our clinics, even those with very weak suspicion of having glaucoma. The most common reason for not being recruited was a lack of manifest glaucoma, 66%, and the second most common reason was too severe visual field defects, 7%.

treated group. Eight patients (3.3%), four in each arm, were lost to follow-up during the first 3 years of the trial. Three patients in the mono-treated group died during the follow-up period, and one was lost just to follow up before the scheduled 3-year follow-up visit due to severe illness and died soon after thereafter. In the multi-treated group, two patients withdrew from the study immediately after their baseline visit and another two died during the follow-up period.

All but four patients attended their 3-year follow-up visits within the accepted time slot of ± 1 month. The visits of three patients were delayed by 1 to 13 days, and the visit of one patient was delayed for 4 months as data collection had to be interrupted due to the COVID-19 pandemic. All patients, except those lost to follow-up, had attended their 3-year follow-up visit by August 2020.

Changes in treatment

During the first 3 years of follow-up, treatment was intensified in 50 (42%) patients in the mono-treated group and in 9 (7%) patients in the multi-treated group (Table 1). Ten patients randomized to monotherapy had very high untreated IOP values. These 10 all returned for an extra visit approximately one week after treatment was initiated. Treatment was increased at the extra visits, most often to a combination drop, in all 10 patients. Eventually one patient underwent trabeculectomy and another iridotomy due to a rapidly progressing cataract with a swelling lens causing an increase in IOP to above 40 mmHg. One monotherapy patient underwent LTP during the first year of follow-up because the eye drops had almost no IOP-lowering effect. The LTP was successful, and the patient refused any further treatment after 12 months in the study, but remained in the study and continued to attend the follow-up visits. The most common reason for increasing treatment was an IOP value, which was considered unacceptably high (n = 40) including the patient described earlier. The second most common reason was that progression of visual field loss was deemed too rapid (n = 10).

In the multi-treated group, treatment was increased in 9 (7%) patients. The most common reason for the first increase in treatment was a combination of rapid progression of visual field loss and unacceptably high IOP (n = 5). Treatment was also increased in this group due to unacceptably high IOP only (n = 2) or rapid progression of visual field loss only (n = 2). Treatment was reduced in 16 (13%) patients in this group; in 15 patients because of adverse events probably caused by the eye drops and in one upon patient request.

Perimetric rate of progression

The median perimetric rate of progression at 3 years was −0.5% /year

Table 1. Changes in treatment.

	Mono-treated, n = 114	Multi-treated, n = 120
Increase in treatment No. of patients (%)	50 (42)	9 (7)
Additional drug	28	2
LTP*	4	–
Additional drug + LTP†	18	7
Decrease in medical treatment No. of patients (%)	1 (0.9)†	16 (13)

*Laser trabeculoplasty.
†One of the four refused any IOP-lowering medication after LTP.

(95% CI: −7.9 to 2.7) in 114 initially mono-treated patients, and −0.1% / year (95% CI: −7.2 to 3.5] in 120 initially multi-treated patients. The rate of glaucomatous progression was significantly more rapid in the mono-treated group than in the multi-treated group (p = 0.03). Distributions of rates of progression are presented in Fig. 2.

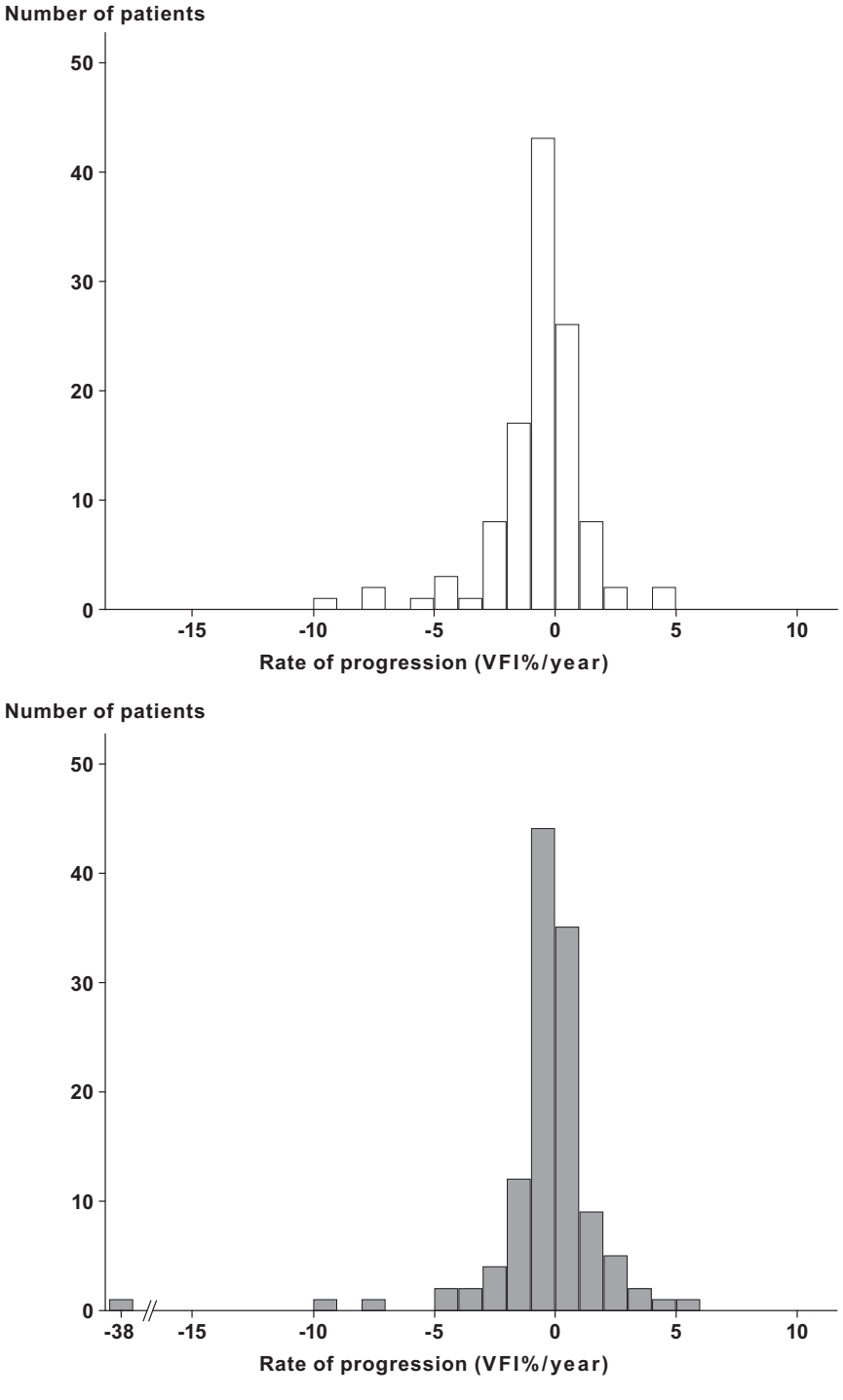

Fig. 2. Distributions of the perimetric rates of glaucoma progression expressed in VFI percentage points per year. Top: Mono-treated patients, n = 114. The distribution was negatively skewed with a median rate of progression of −0.5% /year; 95% confidence limit between −7.9 to 2.7. Bottom: Multi-treated patients, *n* = 120. The distribution was negatively skewed with a median rate of progression of 0.1% /year; 95% confidence limit between −7.2 to 3.2. The outlier on the left of the distribution showed extremely rapid progression due to non-compliance with the prescribed medications and refusal to undergo surgery.

Intraocular pressure

The results of the IOP measurements are given in Fig. 3. The median baseline IOP in the mono-treated group was 24 mmHg (95% CI: 13.7–49.4) and that in the multi-treated group was 24 mmHg (95% CI 13.3–43.7). The median IOP at the 3-year visit was 17 mmHg (95% CI: 9.8–28.1) in the mono-treated group and 14 mmHg (95% CI: 8.0–21.2) in the multi-treated group. The median IOP was almost constant in both treatment groups over the 3-year follow-up period.

Adverse events

In the current report, we have only taken interest in AEs and SAEs deemed to be possibly or probably caused by glaucoma medication (Table 2). In the mono-treated group, 48 AEs were documented in 25 patients (21% of patients) but only in 8 patients while receiving mono-treatment. The AEs in the other 17 patients were reported after treatment had been intensified. Treatment was changed due to AEs in all these patients. No SAEs were reported in the mono-treated group.

In the multi-treated group, 54 AEs were documented in 36 patients (30% of patients) and two SAEs in two other patients. One patient developed bradycardia with syncope but recovered after a fixed-combination drop containing a beta-blocker was withdrawn. The other SAE was in a patient who developed ocular hypotension after starting treatment with a fixed combination of a prostaglandin and a beta-blocker, and a carbonic anhydrase inhibitor in a nonstudy pre-perimetric glaucoma fellow eye with untreated IOP within normal limits. This eye did not develop any macular oedema or choroidal detachment, and the IOP returned to normal after the treatment was withdrawn, but the eye developed a cataract as a consequence. After cataract surgery, the eye exhibited full visual acuity. Changes in treatment as a result of AEs or SAEs were made in 27% of the multi-treated patients.

The relative number of patients with documented AEs was 21% in the mono-treated and 31% in the multi-treated group including the two SAEs.

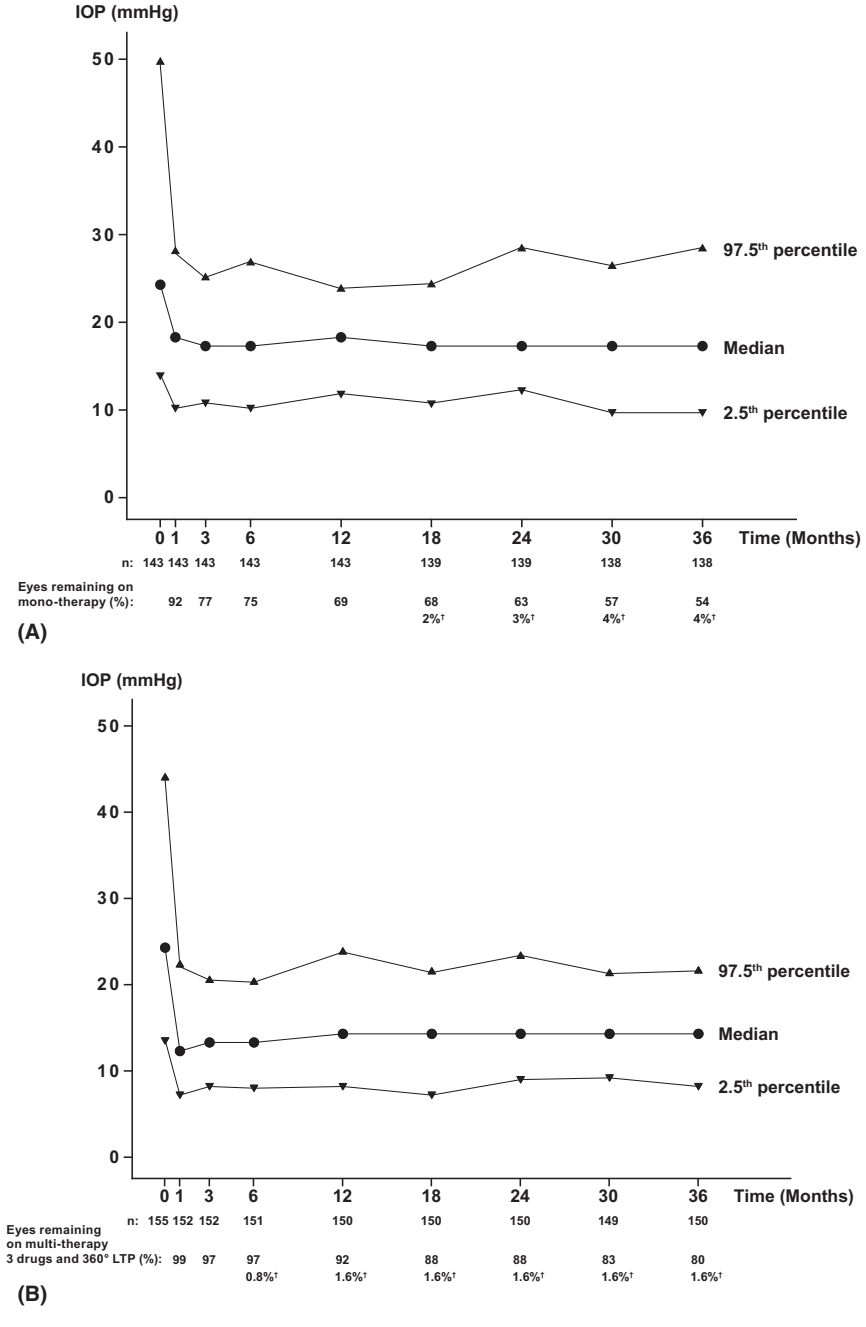

Fig. 3. (A) Course of IOP in initially mono-treated eyes over the 3-year follow-up period. The median IOP at the first scheduled follow-up visit after 1 month was 6 mmHg lower than the median baseline value. This reduction was sustained over time. Treatment had been increased in 12 eyes of 10 patients already before the 1st scheduled follow-up visit after 1 month from baseline. Treatment had been increased in almost half of the patients, leaving 54% still on mono-treatment at the 3-year follow-up visit. † indicates study eyes lost due to patients death during the follow-up. (B) Course of IOP in initially multi-treated eyes over the 3-year follow-up period in multi-treated eyes. Median IOP at the first scheduled follow-up visit after 1 month was 11 mmHg lower than the median baseline value. The reduction was sustained over time, and 80% of all the patients followed up were still on multi-treatment. † indicates study eyes lost due to patients' death during the follow-up.

In the mono-treated group were 48 events documented in 118 patients, or 0.41 event per patient. The corresponding values for the multi-treated patients were 54 AEs plus 2 SAEs among the 122 patients or 0.46 events per patient. The number of patients with general medical inconveniences/disorders reported as possibly or probably caused by glaucoma medication was 18 in the mono-treated group and 15 in the multi-treated group (Table 1).

Discussion

This interim report on the effects of initial treatment intensity on the perimetric rate of progression after 3 years of follow-up was stipulated in the study protocol. The 3-year results revealed that the median rate of glaucomatous progression was slow in both treatment arms but, as expected, significantly faster in the mono-treatment than in the multi-treatment arm. The median perimetric rate of progression in the mono-treated group was −0.5%/year and in the multi-treated group, −0.1% /year. However, the inter-patient variability was high in both treatment arms; the 95% CI ranged from −8.0% to +2.56% /year in the mono-treatment arm and from −6.4% to +3.6% /year in the multi-treatment arm. Although the majority of patients showed no or slow progression, both arms included patients with dangerously rapid progression. Thus, it appears that initial multi-treatment could not prevent the rapid perimetric rate of progression in all patients. One of the multi-treated patients exhibited an extremely rapid rate of progression in one eye. The IOP ranged between 13 and 30 mmHg during the first year of follow-up, the patient made several extra visits including IOP measurements, and treatment was intensified to include four different classes of eye drops and repeated SLT was performed twice, followed by ALT. The patient claimed good compliance in the use of medication, but after some months, it became clear that this patient was not following the recommended treatment. The patient was offered home care sevice to help with the medications but refused the help. Surgery/trabeculectomy was then recommended, and again, the patient refused but finally agreed to be treated with trans-scleral cyclodiode laser.

The average perimetric rate of progression was slower than that previously reported in patients in clinical care. In a previous study of clinical patients with manifest glaucoma, we found a median rate of progression of −0.62 dB /year (Heijl et al. 2013), which corresponds to approximately 1.9% /year in terms of VFI. Similar, but somewhat slower progression rates

Table 2. Adverse events (AEs) and serious adverse events (SAEs) reported as possibly or probably caused by glaucoma medication during the 3-year follow-up period.

	No. of AEs	Mild/moderate/ severe	No. of patients with ≥1 AE	No. of SAEs	No. of patients with ≥1 SAE
Randomized to mono-treatment	48*	30/18/0	25 (21%) 95%CI 15–31%	0	0
Randomized to multi-treatment	54†	35/17/2	36 (30%) 95%CI 22–39%	2‡	2 (1.6%)

CI = confidence interval.

*Four events consisting of vision alteration, 21 of ocular discomfort, three adnexal, and 18 with general medical inconveniences/disorders.

†One event of vision alteration, 18 of ocular discomfort, 20 adnexal, and 15 with general medical inconveniences/disorders.

‡One event of ocular hypotension, one patient with bradycardia with syncope.

have been reported by other groups (Ahrlich et al. 2010; Saunders et al. 2014). In another study, by Chauhan et al. (2014), a median rate of progression of −0.05 dB/year was reported in patients followed up with clinical care, corresponding to approximately −0.15%/year. However, in that study, patients with suspected glaucoma were also included. Differences are expected in the rate of progression between patients in clinical care and patients included in prospective longitudinal studies. Patients included in clinical trials are typically more closely monitored, with a higher frequency of visual field testing, which may result in a slow continued learning pattern with gradually improving visual fields after the first couple of tests. The most important learning effect typically occurs between the first and second visual field tests (Wild et al. 1989; Heijl & Bengtsson 1996), but a continued learning effect has been described (Gardiner et al 2008). A continued learning effect may explain the average positive slope, that is, a small improvement of visual fields, in those not reaching the event of progression outcome over the 2 years of follow-up in the treatment arm of the UK Glaucoma Treatment Study (Garway-Heath et al. 2017). A similar trend, with a median rate of improvement of +0.05 dB /year, was reported in the Canadian Glaucoma Study 3 in patients not showing any progression (Chauhan et al., 2010). In our previous clinical trial, the Early Manifest Glaucoma Trial, the median rate of visual field loss was found to be −0.2 dB /year, that is, ≈ −0.6% /year, in the treatment arm (unpublished results). However, this rate was calculated over a longer time frame, up to 20 years of follow-up, and thus far beyond the stage where small or continued learning effects are likely to affect the results.

The IOP reduction was, as expected, more pronounced in multi-treated patients. The average reduction was about 10 mmHg in the multi-treated group and approximately 7 mmHg in the mono-treated group. The reduction in IOP was almost constant over the 3-year follow-up in both groups. An immediate reduction in IOP of more than 30 mmHg was seen not only among the multi-treated patients but also in a few of the mono-treated patients.

More patients in the multi-treated group had documented AEs and SAEs associated with glaucoma medication than in the mono-treated group, 31 and 21%, respectively. The average number of AEs per patient between the two treatment arms was similar, 0.46 event per patient in the multi-treated group and 0.41 event per patient in the mono-treated group. One would have expected larger differences in the frequency of AEs between the two treatment groups, considering the much more immediate intense treatment in the multi-treated group. The differences in AEs between the two treatment groups might have been more pronounced if more mono-treated patients had maintained their initial treatment throughout the whole 3-year period. However, this would not have been ethically defensible in cases of rapid visual field loss. The GITS protocol allowed for an increase in treatment when deemed necessary by the treating ophthalmologist. This was allowed because there was no upper limit on IOP for inclusion in the study. However, 'unacceptably high IOP' was the most common reason for increasing treatment in the initially mono-treated group, and the treating ophthalmologists were usually generous in increasing treatment. Increased therapy was recommended to 33% of all the patients randomized to monotherapy during the first 3 years of follow-up due only to such 'unacceptably high IOP' with no signs or suspicion of increasing visual field loss.

GITS has several strengths: (1) patients were newly diagnosed and previously untreated; thus, results were not affected by earlier treatment interventions; (2) very low attrition; only two of 242 randomized patients were lost to follow-up for reasons other than death; (3) inclusion of patients diagnosed at all IOP levels. A follow-up period of three years is relatively short, considering that glaucoma is a lifelong disease, and that we plan to predict the risk of developing field defects large enough to affect vision-related QoL during the patients' life expectancy, and the study continues according to initial plans until all patients have been followed up for 5 years. The calculated rates of visual field loss presented in this study were probably affected by continued and small perimetric learning effects as many, 39%, of all eyes had a positive rate of progression with an average improvement of 0.45% per year during these first 3 years of follow-up. The continued learning effect is expected to cease with longer follow-up. It will be interesting to see how the rates of glaucomatous progression have developed after 5-year follow-up.

Potential limitations of GITS are lack of masking; treating physicians were aware of allocated treatment and of visual field outcomes. However, we aimed at mimicking standard glaucoma management by following up the patients according to the Swedish national guidelines (Heijl et al. 2012; Bengtsson et al. 2018), allowing the treating physician to decide on additional visits and change in therapy due to unacceptably high IOP and/or rapid visual field deterioration. Another limitation was that patients with advanced field loss were excluded. Thus our results do not apply to glaucoma patients having severe field loss.

Nevertheless, the current findings suggest that intensive initial IOP-lowering treatment with several drugs results in a slower rate of perimetric progression than conventional

escalating treatment, during the first 3 years after diagnosis, with no large difference in the frequency of adverse events.

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