# What's new in glaucoma? Clinical trials drive practice changes, surgical advancements gather pace

BY ROD MCNEIL

**Rod McNeil** reviews the latest developments in the treatment of glaucoma in the UK.

Primary open-angle glaucoma (POAG), which accounts for over two-thirds of all glaucoma cases, has an estimated UK prevalence in 2017 of approximately 2% of people over the age of 40 years, equating to more than approximately 660,000 people based on 2019 Office for National Statistics (ONS) population projections.

For first-line treatment of chronic open-angle glaucoma, the National Institute for Health and Care Excellence (NICE) recommends a generic prostaglandin analogue [1]. For those who cannot tolerate their current treatment, drugs from another class or preservative-free eye drops should be offered. After trying drugs from two therapeutic classes, practitioners are recommended to consider offering surgery with pharmacological augmentation as indicated or laser trabeculoplasty.

## SLT as a first-line option for newly diagnosed glaucoma or ocular hypertension

A partial update of current NICE glaucoma management recommendations is in progress, reviewing the effectiveness of selective laser trabeculoplasty (SLT) as a first-line treatment compared with intraocular pressure (IOP)-lowering eyedrops for ocular hypertension (OHT) or chronic OAG, with publication expected in January 2022. This follows evidence from the LiGHT clinical trial that SLT is equally effective as eye drops as a first-line treatment for glaucoma or OHT in relation to quality of life (QoL) and clinical outcomes [2].

In the LiGHT trial, similar health-related QoL scores were observed for the SLT and eye drop treatment groups. Both treatment arms had similar endpoints for visual acuities, IOPs and visual field mean deviations. While ~75% of SLT-patients were drop-free at three years, close to one quarter were not. At 93.0% of visits SLT-eyes were within target IOP and this was also the case for the vast majority of drop eyes (91.3%). Topical therapy may nonetheless carry greater risks of glaucomatous deterioration (5.8% vs. 3.8%) and needing trabeculectomy / cataract surgery, although the chances are low.

While SLT may be a cost-effective alternative to drops, topical therapy is an acceptable primary therapy when compared to SLT, with no significant difference in measurable health-related QoL. Another factor is that SLT does not offer immediate lowering of IOP. Considering patient populations encountered in routine clinical practice, of 16,379 patients assessed

**Table 1: Primary and selected secondary outcomes from TAGS (values are mean [SD] unless stated otherwise) at 24 months.**

| Outcomes | Trabeculectomy (n=277) | Medical management (n=226) | Mean difference (95% CI)* | P-value |
|---|---|---|---|---|
| VFQ-25: | | | | |
| Baseline | 87.1 (13.6); n=226 | 87.1 (13.4); n=224 | - | - |
| 24 months | 85.4 (13.8); n=207 | 84.5 (16.3); n=205 | 1.06 (-1.32 to 3.43) | 0.383 |
| Patient's experience (glaucoma getting worse) –No (%): | | | | |
| Baseline | 95/208 (46) | 76/209 (36) | - | - |
| 24 months | 44/196 (22) | 57/194 (29) | 0.70 (0.46 to 1.07) | 0.10 |
| Intraocular pressure, mmHg‡: | | | | |
| Baseline | 19.4 (6.15); n=222 | 19.05 (5.73); n=221 | - | - |
| 4 months | 12.4 (5.73); n=217 | 16.40 (4.12); n=220 | -4.11 (-5.18 to -3.05) | <0.001 |
| 12 months | 11.9 (4.48); n=215 | 16.12 (4.54); n=209 | -4.25 (-5.33 to -3.18) | <0.001 |
| 24 months | 12.4 (4.71); n=206 | 15.07 (4.80); n=202 | -2.75 (-3.84 to -1.66) | <0.001 |
| LogMAR visual acuity‡: | | | | |
| Baseline | 0.15 (0.25); n=227 | 0.17 (0.26); n=223 | - | - |
| 24 months | 0.21 (0.28); n=199 | 0.16 (0.26); n=201 | 0.07 (0.02 to 0.11) | 0.006 |
| Visual field mean deviation, dB: | | | | |
| Baseline | -14.91 (6.36); n=227 | -15.26 (6.34); n=226 | - | - |
| 24 months | -15.15 (6.63); n=202 | -15.42 (6.39); n=200 | 0.18 (-0.58 to 0.94) | 0.65 |

LogMAR; logarithm of mean angle of resolution; VFQ-25, National Eye Institute Visual Function Questionnaire (25 items).
*Mean difference for continuous variables and risk ratios for dichotomous variables.
‡Index eye only.
Source: Adapted from King AJ, et al [6].

for eligibility, 15,661 (94.5%) did not meet inclusion criteria for enrolment in the LiGHT trial.

A retrospective observational study (n=831) from five UK teaching centres found that while most patients initially responded to SLT, the majority failed within one year – treatment success was reported in 70%, 45%, and 27% of eyes at 6, 12 and 24 months post-SLT, respectively [3]. Higher baseline IOP was strongly associated with treatment success (hazard ratio [HR], 0.67 for baseline IOP >21mmHg vs. ≤21mmHg; 95% CI: 0.57–0.80; P<0.001).

## Consultation guideline for angle-closure glaucoma

The role of laser peripheral iridotomy (LPI) is currently under review as part of a new draft clinical guideline on the management of angle-closure glaucoma from the Royal College of Ophthalmologists (RCOphth) and the guideline development group [4]. Around 75% of all UK ophthalmology consultants offer prophylactic LPI to patients with narrow or occluded drainage angles. However, the use of LPI as a preventative treatment in people who are asymptomatic and have never had a documented pressure rise has no firm evidence base. This was confirmed in a randomised controlled trial showing that the benefit of prophylactic LPI is limited, with investigators concluding that widespread prophylactic LSI for primary angle-closure (PAC) suspects is not recommend [5].

For the management of primary angle-closure glaucoma (PACG), it is strongly recommended in the draft clinical guideline that phacoemulsification clear lens extraction (phaco/CLE) be regarded as the definitive intervention for PAC with IOP >30mmHg and PACG [4]. The RCOphth recommends against the widespread, routine usage of prophylactic LPI in the NHS. A group of individuals having additional risk factors may be suitable for prophylactic LPI, named PACS-PLUS. Prompt LPI is recommended for all affected and contralateral eyes when acute (symptomatic) angle-closure has occurred.

## Advanced glaucoma

The multicentre, randomised Treatment of Advanced Glaucoma Study (TAGS) trial, conducted in 27 centres across the UK, represents a landmark achievement, providing the first direct evidence of comparative outcomes with primary trabeculectomy versus primary medical treatment in patients presenting with advanced glaucoma (Table 1) [6]. Advanced disease was classified according to the 'severe' category of visual function (VF) loss using the Hodapp classification of glaucoma severity (Table 2). At 24 months' follow-up, there was no difference noted between treatment arms in the primary outcome, vision specific QoL measured with Visual Function Questionnaire-25 (VFQ-25).

For secondary outcomes, surgery proved to be more effective than primary medication in lowering IOP at all time points measured, and the trabeculectomy arm required far fewer topical medications for control of IOP. At two years, the mean spectral domain (SD) IOP was 12.4(4.7) mmHg and 15.1(4.8)mmHg in the trabeculectomy and medical management arm, respectively. This greater and sustained reduction in IOP (~3-4mmHg) is likely to result in better preservation of visual field over a patient's lifetime, the authors noted.

## Surgical treatment: is fear of 'wipe-out' supported by current evidence?

Guidelines from NICE recommend that people with advanced OAG are offered surgery with pharmacological augmentation as indicated, and offered information on the risks and benefits associated with surgery.

Clinicians are often reluctant to undertake primary surgery for advanced glaucoma because of concerns over perceived high-risk surgical complications related to trabeculectomy [7], notably risks of blindness from bleb related endophthalmitis and 'wipe-out' immediately after surgery.

The so-called 'wipe-out' phenomenon refers to unexplained, catastrophic visual loss after filtering surgery in eyes with advanced glaucoma. Mr Anthony King, Nottingham University Hospital, UK, explored this topic in a presentation during the Glaucoma Subspecialty Day at the 2021 RCOphth Virtual Annual Congress.

A study by Costa et al. considered the incidence and aetiology of visual acuity loss within three months of trabeculectomy [8]. Irreversible loss of central vision soon after the trabeculectomy was noted in four (0.95%) of 508 patients. Older patients, those in whom the visual field preoperatively showed macular splitting and those who had severe hypotony (IOP ≤2 mmHg) on the first postoperative day (P=0.0246) were more likely to experience 'wipe-out'.

A surgical outcome database evaluation showed that trabeculectomy with mitomycin C successfully controls IOP in the short to medium term in patients with advanced glaucoma [9]. Of 103 patients included in the analysis, mean IOP varied between 11.3 and 13.3mmHg between one and seven years' post-trabeculectomy. At year five, 85.2% had an IOP below 16mmHg. Twenty-eight patients experienced a significant reduction in acuity (≥2 lines of Snellen), although this was not due to filtering surgery in the majority. In a case series of 21 consecutive patients with end-stage glaucoma followed for three months after filtering surgery, IOP was reduced effectively and vision was preserved with no occurrences of 'wipe-out' phenomenon [10].

A prospective evaluation of early visual loss after glaucoma surgery in eyes with split fixation found that visual loss after surgery in advanced glaucoma is rare and most often because of reversible causes [11]. None of the eyes in this interventional cohort developed a loss of central vision. A clinical cohort study and meta-analysis evaluating the influence of glaucoma surgery (Baerveldt implant or trabeculectomy) on visual function reported no surgery-induced changes in BCVA. The authors concluded that, on average, the benefit (long-term preservation of the visual field) of glaucoma surgery surpassed the cost (loss of visual function associated with the procedure) after approximately 1.5 years [12].

**Table 2: Advanced glaucoma: Classification of 'severe' visual field (VF) loss.**

| **Advanced glaucoma: severe VF loss using the Hodapp classification of glaucoma severity** |
|---|
| Severe glaucomatous VF loss (Hodapp classification) in one or both eyes at presentation on any of these criteria:<br>a) Mean deviation ≤12.00 dB.<br>b) >50% of points defective in the pattern deviation probability plot at the 5% level (>27 points on 24-2 HVF).<br>c) >20 points defective at the 1% level.<br>d) A point in the central 5 degrees has a sensitivity of 0 dB.<br>e) Points within 5 degrees of fixation<15 dB sensitivity in both upper and lower hemifields. |

Source: Adapted from King AJ, et al. *Br J Ophthalmol* 2018;**102(7)**:922-8.

The TAGS study reported that no unexplained loss of vision occurred immediately after surgery, indicating no occurrence of 'wipe-out' [6]. While severe vision loss as a consequence of trabeculectomy surgery did not occur, two patients developed endophthalmitis, one in each study arm and both were treated with intravitreal antibiotics and had good visual recovery.

Mr King noted that most reports of 'wipe-out' following glaucoma surgery are from retrospective studies and the phenomenon is defined differently in different studies. Reported numbers, however, are low. Catastrophic unexplained loss of vision following uncomplicated trabeculectomy surgery has not been reported in any recent prospective studies of patients with advanced glaucoma. If the 'wipe-out' phenomenon after filtration surgery exists, it is exceedingly rare, observed Mr King.

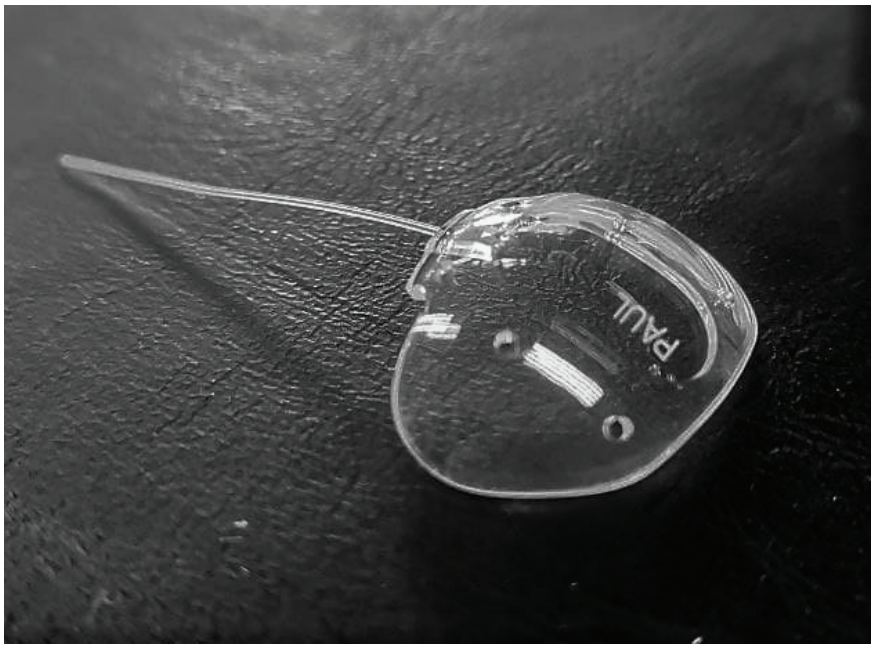

Figure 1: The PAUL glaucoma drainage device. Image courtesy of Advanced Ophthalmic Innovations.

## MIGS devices: evidence-based momentum

A survey of glaucoma surgical practices in the UK following the onset of the COVID-19 pandemic suggests that trabeculectomy is being performed with reduced frequency [13]. Although trabeculectomy was the procedure of choice for most (87%, 61/70) glaucoma specialists, favoured alternative procedures appear to be conventional diode laser, glaucoma drainage devices, deep sclerectomy and Preserflo microshunt (Santen). The most commonly performed minimally invasive glaucoma surgery (MIGS) procedure in the 12 months before COVID-19 was the iStent inject (Glaukos), followed by ab externo devices XEN 45 (AbbVie/Allergan) and Preserflo, with a large proportion of respondents (73%) reporting performing alternative surgical techniques as part of their glaucoma armamentarium. Guidelines from the European Glaucoma Society state that only ab interno non-bleb forming procedures can be defined as minimally invasive glaucoma surgery [14].

Implantation of the iStent inject device at the time of phacoemulsification is a safe and effective method to decrease IOP and the need for antiglaucoma medications in patients with mild-to-moderate POAG and cataract [15,16]. Two-year outcomes from the pivotal trial of iStent inject trabecular micro-bypass in POAG and cataract show significant IOP reductions across all levels of baseline diurnal IOP and medication burden. Intraocular pressure reductions increased with higher baseline IOP and remained stable across all levels of preoperative medication, suggesting the potential utility of the iStent inject in more medically challenging cases [17].

A prospective analysis of outcomes at 12 months in patients implanted with two iStent inject devices combined with phacoemulsification reported surgical outcomes are positively associated with device protrusion within the anterior chamber, suggesting that Schlemm canal dilatation has a favourable prognostic value [18]. The evaluation showed that the iStent inject devices do not move within the first year after implantation. Unmedicated IOP ≤18mmHg was achieved in 58.98% of operated eyes.

A Cochrane review of ab interno trabecular bypass surgery with Schlemm's canal microstent Hydrus (Ivantis, Inc.) for OAG concluded that, in people with cataracts and generally mild to moderate OAG, there is moderate-certainty evidence that the Hydrus microstent with cataract surgery compared to cataract surgery alone, likely increases the proportion of participants who do not require IOP-lowering medication, and may further reduce IOP at short- and medium-term follow-up [19].

Published three-year outcomes from HORIZON showed that combined cataract surgery and Hydrus microstent placement for mild to moderate POAG is safe, more effective in lowering IOP with fewer medications, and less likely to result in further incisional glaucoma filtration surgery than cataract surgery alone [20]. Five-year follow-up data confirmed a significant reduction in need for invasive filtration surgery (cumulative probability of reoperation 2.5% with cataract surgery and Hydrus implant vs. 6.4% with cataract surgery only) and subsequent glaucoma medication (65% medication free five-years post-implant) [21].

Twelve-month results from the COMPARE prospective randomised trial – the first study to directly compare the efficacy of different MIGS devices for use in glaucoma management without concurrent cataract surgery – demonstrate standalone MIGS with the Hydrus microstent resulted in a higher surgical success rate and fewer medications compared with the 2-iStent procedure [22]. Secondary glaucoma surgery was performed in two eyes in the 2-iStent group and in none of the Hydrus eyes. Alcon announced November 2021 its intention to acquire Ivantis, Inc. and its Hydrus microstent, entailing an upfront consideration of $475 million. The deal affirms Alcon's commitment to 'the surgical glaucoma space' and strengthens its global ophthalmology portfolio.

Study results evaluating the effectiveness of the Preserflo microshunt implant in glaucoma patients confirm a positive experience. In one retrospective, European multicentre study, through month 12, mean IOP was lowered significantly from 25.1 ±6.5mmHg at baseline to 14.1 ±3.4mmHg ($P<0.0001$), with medication use significantly reduced from 3.0 ±1.0 medications preoperatively to 0.77 ±0.95 medication ($P<0.001$) [23]. A comparative outcomes study among a cohort of POAG patients (n=52) found that both Preserflo microshunt and trabeculectomy were equally effective and safe in lowering mean diurnal IOP at six months [24]. Sustained reductions in mean IOP and medications for up to five years post-Preserflo microshunt implantation were noted in an extension study (n=23) [25].

The PAUL glaucoma drainage device (Advanced Ophthalmic Innovations) is a new aqueous shunt device demonstrating comparable efficacy to other available implants in eyes with refractory glaucoma (Figure 1) [26]. Early outcome data from Manchester Royal Eye Hospital show that the PAUL glaucoma implant significantly reduces IOP and medication use, with few intraoperative and postoperative complications [27]. Among a consecutive cohort of 99 eyes of 97 patients who had surgery with the PAUL glaucoma implant (between February 2019 and May 2020, under the supervision of five consultant surgeons), nine cases (9.3%) were deemed failures (six had <20% IOP reduction from baseline and three had IOP >21mmHg). The mean±SD preoperative IOP was 28.1 ±9.0mmHg, decreasing to 13.6 ±4.7mmHg at six months. At one year, mean IOP was 13.3 ±4.4 and the mean change in number of medications was a reduction of 2.38 ±1.48 (n=52). There were two cases of hypotony. A uniform standardised surgical technique was used: 6/0 Prolene® intraluminal stent without any Vicryl® overtie or use of viscoelastic, allowing immediate drainage and a more predictable IOP outcome within the first few weeks.

**Novel-acting medical treatment**

Netarsudil 0.02% (Rhokiinsa, Aerie Pharmaceuticals) is a potent Rho kinase / norepinephrine transporter inhibitor acting by increasing the trabecular outflow, decreasing the aqueous production, and possibly decreasing the episcleral venous pressure. Fixed-combination netarsudil–latanoprost (Roclanda, Aerie Pharmaceuticals) was approved by the European Commission in January 2021 and received marketing authorisation from the UK Medicines and Healthcare products Regulatory Agency (MHRA) in April 2021. It is indicated for the reduction of elevated IOP in adult patients with POAG or OHT for whom monotherapy with a prostaglandin analogue or netarsudil provides insufficient IOP reduction.

In two main studies, IOP reductions in patients treated with Roclanda were significant and clinically relevant and were statistically superior to IOP reductions achieved by netarsudil and latanoprost monotherapy [28]. In Mercury 3, a phase3b non-inferiority trial, treatment with Roclanda demonstrated non-inferiority to fixed-combination bimatoprost and timolol (Ganfort, Allergan) across nine of nine timepoints over 90 days, with an average IOP reduction from baseline of approximately 37%.

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(All links last accessed November 2021)


**AUTHOR**

**Rod McNeil,**

Independent Journalist and Consultant.