

TAGS trial summary findings

Professor Anthony King Consultant glaucoma specialist ophthalmologist, Honorary professor clinical ophthalmology, Chairman of Glaucoma UK, Nottingham University Hospital

Introduction

Advanced glaucoma has a serious impact on numerous aspects of daily living affecting independent living. Primary Open Angle Glaucoma (POAG) affects around 2% of the population over 40 years of age, increasing with age. In the United Kingdom glaucoma is the second commonest cause for certification as visually impaired.

As glaucoma is asymptomatic in its early phases, people are often unaware of its onset, resulting in presentation with advanced disease. Presentation with advanced glaucoma is the main risk factor for progression to blindness¹, in the UK around 25% of patients with glaucoma present with advanced disease².

Reducing intraocular pressure (IOP) is the only proven treatment for glaucoma. Better IOP control at an early stage reduces the risk of further progression. In the UK, the National Institute for Health and Care Excellence (NICE) guidelines suggest patients presenting with advanced disease should be offered trabeculectomy as a primary intervention. However most UK ophthalmologists don't follow this guidance and treat patients medically with escalating drop therapy³, offering trabeculectomy if this is unsuccessful. This approach is due to the poor evidence supporting primary trabeculectomy and concern regarding surgical complications. However, clinicians indicated high quality evidence would change their practice³.

Methods

Study design: A multi-centre, parallel group, open label, pragmatic RCT in 27 hospitals in the UK.

Participants: Adults with severe glaucoma according to the extent of visual field (VF) loss (Hodapp-Parrish-Anderson classification) in one or both eyes at presentation. Inclusion criteria was diagnosis of OAG (including pigment dispersion glaucoma, pseudoexfoliative glaucoma and normal tension glaucoma).

Randomisation and masking: Participants were randomly assigned to trabeculectomy or medical management. IOP measurement was masked to the intervention, VF assessment was undertaken using the Humphrey Visual Field (HVF) analyser 24-2 Sita Standard algorithm and evaluation was undertaken by an independent reading centre unaware of allocation of participants.

Procedures: Participants allocated to trabeculectomy were placed on the National Health Service (NHS) waiting list and continued holding medication until trabeculectomy was undertaken.

Participants allocated to medical treatment underwent an escalating medical management regimen in accordance with accepted standard of care (NICE). Escalation of medical management was based upon the judgement of the treating clinician. If IOP control was deemed inadequate on maximum medical therapy, trabeculectomy was offered.

Outcomes: The primary outcome was vision-related quality of life measured with the Visual Function Questionnaire-25 (VFQ-25). Other patient reported outcomes measured with the EQ-5D-5L, Health Utility Index-mark 3 (HUI-3), Glaucoma Utility Index (GUI), VFQ-25 and patient experience were secondary outcomes.

Clinical effectiveness outcomes were IOP, LogMAR Visual Acuity (VA), glaucoma severity according to VF MD, need for cataract surgery, accordance with visual standards for driving, eligibility for sight impairment certification and safety of interventions. These were measured at baseline, 4, 12, 24 and 60 months. Adverse events (AEs) were recorded at all times.

Results

453 participants from 27 hospitals were allocated to either trabeculectomy (227) or medical management (226). In the trabeculectomy arm, 201 (88.5%) participants received trabeculectomy in their study eye.

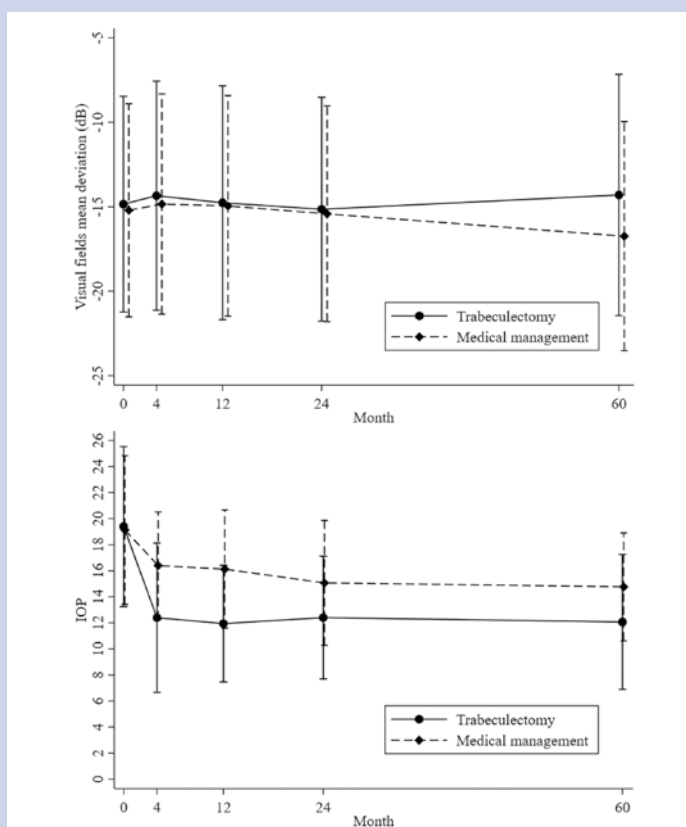
There was no difference between arms at baseline. At five years, there was no difference for the primary outcome the VFQ-25, but VFQ-25 subscale analysis indicated those in the medical arm were less likely to be driving at 5-years [$P < 0.04$]. There was no difference between arms for any of the other quality of life outcomes measured (GUI, EQ5D, HUI-3).

The mean IOP at five years was 12.07 (SD 5.18) for the trabeculectomy arm and 14.76 (SD 4.14) for the medical arm ($p < 0.001$), this translated into a clinically meaningful difference in disease (VF) progression between arms at 5-years of nearly 2dB MD favouring trabeculectomy (MD trabeculectomy arm -14.30 (7.14) dB, MD medical arm -16.74 (6.78) dB, ($p < 0.001$).

In total, 115 (52.2%) participants in the trabeculectomy arm and 124 (57.9%) in the medical arm had a safety event: relative risk 0.92, 95% CI (0.72 to 1.19), p -value 0.54. Two participants developed endophthalmitis, one in each arm of the study, and four participants lost more than 10 letters of LogMAR VA, three in the trabeculectomy arm and one in the medical arm, there were no episodes of wipeout following trabeculectomy.

In the medical arm, 48 participants (21%) required a trabeculectomy for IOP control. The frequency of additional interventions following trabeculectomy, such as bleb revision, AC reformation and bleb re-suturing was proportionate to the number of trabeculectomies undertaken in each arm. In the trabeculectomy arm, trabeculectomy failure required further surgery in the form of glaucoma drainage devices in four participants.

At five years, 35.4% (62/175) participants required IOP lowering drops in the trabeculectomy arm and 72.5% (124/171) in the medical arm [RR 0.48 95% CI (0.34 to 0.67); p -value < 0.001]. The mean number of drops required was 0.64 (1.01) and 1.54 (1.21) in the trabeculectomy and medical arms, respectively.



Discussion

At 5-years, initial surgery was associated with better IOP control and less disease progression. Trabeculectomy required fewer topical medications for IOP control. Adverse events, including serious adverse events, between arms were similar⁴.

The IOP-lowering achieved in the trabeculectomy arm is consistent with current results reported from the NHS by Kirwan⁵ and by Stead⁶ who specifically reported IOP lowering in eyes with advanced VF loss.

There was a clinically important difference in disease progression, with those in the trabeculectomy arm having almost 2dB less visual field loss compared with initial medicine after 5-years. TAGS is the first trial to report a beneficial effect of primary surgery compared with medication regarding disease progression in patients presenting with advanced disease. Reduced VF progression is particularly important in people with severe disease as they have less visual field reserve.

For patients, the most important outcome of glaucoma management is their ability to continue to live an independent life and maintain their QoL. There was no QoL difference between the interventions at 5-years which will help inform patients when considering their treatment options.

A major concern for clinicians was the perceived risk of surgery complications³, specifically the risk of unexplained catastrophic vision loss immediately after surgery (termed 'wipeout') and the risk of long-term complications and sight loss associated with trabeculectomy³. At five years there was no evidence to support these concerns. Additional surgery was required in both arms. In the medical arm 48 (21.4%) participants had undergone trabeculectomy by five years and 8% of the trabeculectomy group required intervention to manage clinically significant hypotony. The potential need for additional surgery interventions should be highlighted to patients in both groups when considering the treatment options.

	Trabeculectomy N=227	Medical management N=226
Number of participants with a safety event	117 (53.4) RR 0.90	124 (57.9) p=0.43
AE's		
Number of participants	110	108
Number of events	224	223
Details		
Drop related	28	97
Ocular surface related	48	55
Non-specific	35	29
Hypotony requiring intervention	15	5
Potential AE related to surgery	13	8
Glaucoma progression	3	12
Hypotony requiring intervention	15	5
Early bleb leak	13	3
Choroidal effusion	9	4
Shallow anterior chamber	8	3
Ptosis	7	3
Irreversible loss of ≥ 10 ETDRS letters	5	3
Corneal epithelial defect	4	-
Hyphaema	4	-
Late bleb leak	4	-
Cataract	1	2
Conjunctival buttonhole	3	-
Macular oedema	1	1
Suprachoroidal haemorrhage	2	-
Blebitis	2	-
Endophthalmitis – endogenous	1	-
Endophthalmitis – bled related	-	1
Persistent uveitis	1	-
Retinal detachment	-	-
Non-specific unrelated uveitis	1	-
Number requiring additional intervention, n	76 RR 0.68	96 p-value 0.014
Cataract surgery	58	56
Bleb revision	11	2
Ac reformation	5	3
Bleb resuturing	6	1
Trabeculectomy	-	48
Further glaucoma surgery/drainage device	15	17

Conclusion

At five years TAGS demonstrated that primary trabeculectomy is more effective in lowering IOP and preventing disease progression than primary medical treatment in patients presenting with advanced disease and has a similar safety profile. Trabeculectomy should be offered as a primary intervention in patients presenting with advanced glaucoma.

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