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One Year of Glaucoma Research in Review: 2012 to 2013

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Abstract

Purpose—The objective of this study was to provide the practicing clinical ophthalmologist with an update of pertinent glaucoma literature published from 2012 to 2013.

Design—Literature review.

Methods—The authors conducted a 1-year (July 1, 2012, to September 30, 2013) English-language glaucoma literature search on PubMed using the following terms: glaucoma, automated perimetry, optic nerve imaging, optical coherence tomography, glaucoma structure and function, intraocular pressure, central corneal thickness, glaucoma medical therapy, neuroprotection, glaucoma laser treatment, secondary glaucoma, glaucoma surgery, and miscellaneous topics in glaucoma.

Results—Of 2659 articles on glaucoma published during our time frame, this review selected original and review articles that reflect novel aspects and updates in the field of glaucoma, while excluding letters to the editor, unpublished works, and abstracts. Preference was given to human research.

Conclusions—This review focuses on literature that is applicable to ophthalmologists in practice and also highlights studies that may enhance the diagnosis and management of glaucoma.

Keywords

glaucoma; review; optical coherence tomography; intraocular pressure; glaucoma medications; neuroprotection; glaucoma surgery

A multitude of studies focused on enhancing the diagnosis, treatment, and understanding of glaucoma were described and published over the past calendar year. Many of these studies were aimed at improving the utility of automated perimetry in the early detection of glaucoma progression and analyzing the retinal nerve fiber layer (RNFL) using optical coherence tomography (OCT). In addition, great attention was given to the efficacy of fixed combination medications as well as surgical protocols and techniques aimed at optimizing patient outcomes.

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This review highlights a select number of articles that appeared in the English literature over the past year. Included articles were listed in PubMed between July 1, 2012, and September 30, 2013. Large, prospective, randomized trials in humans were given preference for inclusion. The overriding consideration in the selection of specific articles was the desire to include clinically relevant, novel, and potentially important original research.

GLAUCOMA MORBIDITY AND COMPLICATIONS

In order to gain a better understanding of the rate of blindness among patients with glaucoma, Peters and colleagues[1] performed a retrospective review on a group of 592 Swedish glaucoma patients who died between January 2006 and June 2010. At the time of their last visit, 250 patients (42.2%) had at least 1 blind eye from glaucoma, whereas 97 patients (16.4%) were bilaterally blind, and 12 patients (0.5%) had low vision. The cumulative incidence of unilateral and bilateral blindness from glaucoma after 10 years was 26.5% and 5.5%, respectively, which increased to 38.1% and 13.5% at 20 years. The median age at onset for bilateral blindness was 86 years, whereas the median duration of bilateral blindness was 2 years. Blindness was defined using World Health Organization criteria (visual acuity <20/400 and/or central visual field <10 degrees).[1]

Peters et al[2] also studied a population of 423 patients with primary open-angle glaucoma (POAG) and pseudoexfoliation glaucoma and found that the 64 patients who went blind had a longer mean duration of diagnosed disease (14.8 ± 5.8 vs 10.6 ± 6.5 years; $P < 0.001$). Furthermore, the risk of blindness increased with higher intraocular pressure (IOP) (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.03–1.13), each stage of advanced field loss at the time of diagnosis (OR, 1.80; 95% CI, 1.34–2.41), and older age at death (OR, 1.09; 95% CI, 1.03–1.14).[2]

The effects of glaucoma extend beyond visual manifestations. Wang et al[3] examined the burden of glaucoma on sleep quality through the use of a validated self-rated questionnaire. They found that the prevalence of sleep disturbances was higher in both POAG and primary angle-closure glaucoma (PACG) groups compared with control. Interestingly, more patients with PACG between the ages of 61 and 80 years experienced problems than did those with POAG in the same age group. They did not find a significant correlation between the prevalence of sleep disturbances and the severity of visual field loss or IOP.[3]

The Central India Eye and Medical Study demonstrated differences in both lumbar cerebrospinal fluid pressure (CSFP) and translamina cribrosa pressure between individuals with and without glaucoma. The difference in CSFP was more pronounced in open-angle glaucoma compared with angle-closure glaucoma (3.0 vs 1.8 mm Hg), whereas differences in IOP were higher in angle-closure glaucoma (8.5 vs 3.0 mm Hg). The presence of open-angle glaucoma was significantly associated with translamina cribrosa pressure (OR, 1.24; 95% CI, 1.19–1.29; $P < 0.001$) but not with IOP (OR, 0.96; 95% CI, 0.91–1.00; $P = 0.08$), supporting the hypothesis implicating low CSFP in the pathogenesis of open-angle glaucoma.[4]

Based on studies showing that patients with both Alzheimer disease and normal pressure hydrocephalus are at a higher risk of developing glaucoma, Wostyn and colleagues[5]

performed a literature review to hypothesize that age-related changes in the circulatory pattern—and decreased turnover—of cerebrospinal fluid are responsible for the development of normal-tension glaucoma (NTG).

AUTOMATED PERIMETRY

In order to compare 10-2 and 24-2 visual field testing in detecting the progression of initial parafoveal scotomas, Park et al[6] performed a retrospective observational study composed of 50 eyes of 50 glaucoma patients. Significantly more progressing eyes were detected using 10-2 than 24-2 analysis (24 vs 11 eyes; $P = 0.007$), suggesting that closer surveillance of the central visual field is warranted in this population of patients.[6]

Does glaucoma progression occur in a linear fashion? Pathak et al[7] found that nonlinear exponential models provided significantly better fits for performing trend analysis on longitudinally collected perimetry data compared with linear models ($P < 0.0001$). Of note, these nonlinear models avoided significant autocorrelation, provided residuals that trended toward normal distributions, and improved homogeneity.[7]

Fan and colleagues[8] examined risk factors associated with progressive visual field loss in PACG using 89 eyes of 89 Chinese patients and found that only shorter axial length was associated with visual field progression, whereas age, follow-up duration, anterior chamber depth, and IOP were not significantly correlated.

OPTIC NERVE IMAGING

Lloyd and colleagues[9] examined disc photographs in a group of 336 eyes of 168 patients with ocular hypertension or early glaucoma and found that 27.4% of eyes exhibited progression after a median of 6.1 years. Of the eyes with progression, excavation was seen in 89%, rim thinning in 54%, and notching in 16%. The most common location of change was in the inferotemporal quadrant of the disc, although 30% of cases exhibited progression in more than 1 location.[9]

In assessing the optic nerve, Tatham et al[10] postulated a nonlinear relationship between retinal ganglion cell (RGC) estimate and cup-to-disc ratio. They concluded that cup-to-disc ratio is not sensitive for evaluating progressive neural losses in glaucoma, as small changes can be associated with large losses of RGCs.[10]

Zangwill et al[11] performed a longitudinal randomized clinical trial encompassing 832 eyes of 441 subjects in the Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study. In the 66 eyes that developed POAG, the rate of rim area loss was significantly higher than those that did not (univariate mean, −0.0131 vs −0.0026 mm^2/y). In multivariate analyses, the rate of rim area loss and other topographic parameters were also significantly higher in eyes with worse baseline visual field pattern SDs and elevated IOPs. Furthermore, the rate of rim area loss in eyes with an optic disc POAG end point was significantly higher than that in those with a visual field POAG end point.[11]

Given the recent advancement of spectral domain OCT (SD-OCT), Chauhan and Burgoyne[12] highlighted its importance in assessing the optic nerve head (ONH) to account for eye-specific differences in the anatomy and geometry of the nerve and fovea. In particular, their approach was designed to enhance the consistency of rim width, as well as peripapillary and macular thickness measurements.[12] When using SD-OCT, it is possible that changes in the angle of acquisition (or parallax) between tests can contribute to test-retest variability. Lee and colleagues[13] found that correcting for the retinal angle provided better reproducibility of peripapillary RNFL thickness (intraclass correlation coefficient, 0.990; 95% CI, 0.983–0.944) compared with a non–angle-corrected algorithm (intraclass correlation coefficient, 0.964; 95% CI, 0.940–0.979).

In a study consisting of 89 eyes with open-angle glaucoma, Mayama et al[14] demonstrated that an averaged RNFL thickness calculated over multiple grid sizes in the peripapillary region exhibits greater sensitivity and specificity (0.94 and 0.96, respectively) than alternative methods such as the annulus and circle methods.

The population-based Beijing Eye Study 2011 consisted of 3468 patients (age range, 50–93 years) who underwent SD-OCT imaging. Localized RNFL defects were detected in 640 eyes (9.9% ± 0.4%) of 479 subjects (14.8% ± 0.6%). Retinal nerve fiber layer defects—which were found to be associated with glaucoma, nonglaucomatous optic nerve damage, and diabetic retinopathy—had an increased prevalence in those patients with advanced age, myopia, and large peripapillary A zones.[15] Similarly, the EPIC-Norfolk Eye Study found that older age, male sex, shorter axial length, and pseudophakia were all associated with thinner RNFL values following adjustment for potential confounders.[16]

In order to compare their diagnostic utility, Koh et al[17] compared the peripapillary RNFL thickness measurements obtained using Cirrus high-definition OCT (HD-OCT) (Carl Zeiss Meditec, Dublin, Calif) and spectral OCT/scanning laser ophthalmoscopy (SLO) (OPKO/OTI, Miami, Fla). The area under the receiver operating curve (AUROC) of RNFL thickness for the discrimination of glaucoma did not differ significantly between the devices ($P > 0.05$), although spectral OCT/SLO yielded greater AUROCs for nasal RNFL thickness ($P < 0.05$). They also found that the RNFL thickness measured by spectral OCT/SLO was greater than that obtained using Cirrus HD-OCT ($P < 0.001$).[17] Akashi and colleagues[18] found that Cirrus, RTVue, and 3-dimensional OCT all exhibited similar abilities to detect glaucoma, although RTVue showed the best diagnostic utility for the nasal circumpapillary RNFL and ganglion cell complex thicknesses.

Amid growing evidence that early glaucomatous changes involve the macula, Hood and colleagues[19] utilized frequency domain OCT to demonstrate that the RGC and inner plexiform layers preferentially undergo greater degrees of thinning within the inferior retina in glaucoma patients. This finding is significant, as these changes can be missed with standard visual field protocols implementing a 6-degree grid, such as the 24-2 test pattern.[19]

In contrast, Jeoung et al[20] compared macular ganglion cell–inner plexiform layer, peripapillary RNFL thickness, and ONH parameters on a group of 306 glaucoma patients using Cirrus HD-OCT and did not find any significant differences in AUROC, indicating

that each of these maps has comparable diagnostic utility in the detection of glaucoma. Kiddee et al[21] utilized SD-OCT to find that parameters based on circumpapillary RNFL thickness—the thickness of the inferior quadrant in particular—have more diagnostic utility than those based on the macula in distinguishing between healthy, glaucoma suspect, and glaucomatous eyes.

Although these studies emphasize the importance of RNFL thickness, Fortune and colleagues[22] used a macaque glaucoma model to show that progressive loss of RNFL retardance occurs earlier and with more frequency than RNFL thinning.

Furlanetto et al[23] performed enhanced depth imaging OCT B-scans of the ONH and found that the mean and maximum lamina cribrosa depths were significantly greater in glaucomatous eyes compared with normal ($P < 0.03$). This difference was upheld between individuals and also between eyes of patients with unilateral glaucoma.[23]

Imaging of the optic nerve and its associated pathways are not limited to the eye. El-Rafei and colleagues[24] described the use of diffusion tensor neuroimaging analysis of the visual pathway fibers in the optic radiation for detecting glaucoma and discriminating between different glaucomatous entities. Using their system, they reported a classification accuracy of 92.4% in distinguishing between normal and POAG groups and 100% in cases of healthy and NTG groups. Furthermore, they also found that the system could differentiate between POAG and NTG with 98.3% accuracy.[24] Similarly, Chen et al used 3-dimensional magnetic resonance imaging technology to demonstrate significant differences in the gray matter volume of specific areas within the brain between patients with advanced POAG and healthy subjects.[25]

STRUCTURE AND FUNCTION

Lamparter and colleagues[26] investigated the structure-function relationship in glaucoma by manually tracing individual RNFL bundles to the ONH and superimposing a 24-2 visual field grid pattern. They found that the influence of ocular parameters could be evaluated for 33 of 52 visual field locations. The position of the ONH in relation to the fovea was the most prominent predictor for variations in the mapping of retinal locations to the ONH.[26]

In order to assess the utility of RGC counts in predicting progression, Meira-Freitas and colleagues[27] followed 288 eyes of 288 patients suspected of having glaucoma for a total of 3.8 ± 1.0 years. Of the 48 eyes that showed progression during the follow-up period, the mean rate of change in estimated RGC counts was −18,987 cells/y in progressors and −8808 cells/y in nonprogressors ($P < 0.001$). Baseline RGC counts (hazard ratio [HR], 1.56 per 100,000 cells lower; 95% CI, 1.18–2.08; $P = 0.002$) and slopes of RGC loss (HR, 2.68 per 10,000 cells/y; 95% CI, 1.22–5.90 cells/y; $P = 0.014$) were significantly predictive of progression. In addition, the longitudinal model including estimates of RGC counts performed significantly better than models including only structural or functional indexes.[27]

Le and colleagues[28] utilized Fourier-domain OCT to map the macula and peripapillary regions of the retina in 56 eyes of 38 glaucoma patients. They ultimately found significant point-specific and regional correlations between ganglion cell complex loss, nerve fiber

layer loss, and deficits on standard automated perimetry, respecting the arcuate course of the RNFL in the macula.[28]

INTRAOCULAR PRESSURE

Kim and colleagues[29] compared the accuracy of rebound tonometry with Goldmann applanation tonometry and found good correlation in IOP measurements ($r = 0.6995$; $P < 0.001$). Although the IOP measured by rebound tonometry tended to be higher (mean, 1.92 ± 3.29 mm Hg; 95% limit of agreement, −4.52 to 8.37 mm Hg), this difference did not vary based on central corneal thickness (CCT, age, axial length, or spherical equivalent.[29] In contrast, Dahlmann-Noor et al[30] found poor agreement between the 2 methods when tested in children.

Lee and colleagues[31] performed a retrospective chart review in a group of 49 eyes of 49 patients with NTG and IOP of 15 mm Hg or less, and 49 eyes of 49 NTG patients with IOP greater than 15 mm Hg. They found that the mean IOP and IOP fluctuation were significantly greater in those with IOP greater than 15 mm Hg ($P < 0.001$ and $P = 0.016$). Using multivariable analysis, they also found that visual field progression was significantly associated with disc hemorrhage in those with IOP 15 mm Hg or less (HR, 6.19; $P = 0.017$) and mean IOP in those with IOP greater than 15 mm Hg (HR, 1.77; $P = 0.029$), reflecting differential contributions from both IOP-dependent and IOP-independent factors to visual field progression.[31]

Moghimi and colleagues[32] evaluated the effect of cataract surgery on IOP in filtered eyes with PACG and found that surgery decreased IOP from 18.16 ± 5.91 mm Hg to 15.37 ± 2.90 mm Hg ($P < 0.01$) and also decreased the mean number of glaucoma medications from 1.81 ± 0.24 to 0.86 ± 1.00 ($P = 0.001$) at the 1-year postoperative mark. Furthermore, they found that the magnitude of IOP reduction is greater in patients with higher preoperative IOP ($r = 0.85$; $P < 0.001$) and more shallow anterior chambers ($r = −0.38$; $P = 0.01$).[32]

CORNEAL THICKNESS AND BIOMECHANICS

Lu et al[33] performed a meta-analysis on more than 20,000 individuals in European and Asian populations that identified 16 new loci associated with CCT. Of these, only 1 polymorphism (FNDC3B) was associated with POAG ($P = 5.6 \times 10^{-4}$) when tested in 3 cohorts, suggesting that although CCT is a risk factor for POAG, this correlation may not have a genetic basis.[33]

Hoffmann and colleagues[34] examined the distribution of CCT in a German cohort composed of 4698 enrollees. They found that mean CCT was slightly higher in men than in women (557.3 ± 34.3 vs 551.6 ± 35.2). In addition, univariable linear regression showed that IOP was correlated with CCT ($P < 0.0001$). Multivariable linear regression analysis revealed correlations between gender, spherical equivalent, and CCT.[34]

To evaluate the role of corneal hysteresis as a risk factor for visual field progression among glaucoma patients, Medeiros et al[35] examined a group of 114 eyes of 68 glaucoma patients and found that each 1–mm Hg lower corneal hysteresis was associated with 0.25%/y higher

rate of visual field index decline over time ($P < 0.001$). In addition, multivariable models showed that the effect of IOP on progression rates was dependent on hysteresis—eyes with elevated pressure and low hysteresis were at an increased risk of having accelerated progression rates.[35]

Razeghinejad and Banifatemi[36] did not find any statistically significant difference in CCT, axial length, anterior chamber depth, and lens thickness using ultrasound biometry between eyes with PACG and angle-closure suspects. However, they found that larger lens-axial length factor ($P < 0.0001$) and CCT ($P = 0.001$) were significant risk factors for acute primary angle closure (PAC).[36]

Guzman et al[37] utilized OCT of the anterior segment to investigate differences between patients with PAC, PACG, previous acute PAC, and angle-closure suspects. Ultimately, they found that eyes with APAC had the most narrow angles, smallest anterior segment dimensions, thickest iris, and largest lens vault among the groups.[37]

PHARMACOLOGIC INTRAOCULAR PRESSURE LOWERING

As fixed combinations of pharmacologic agents may help improve compliance and ease the burden of chronic use, their use has become increasingly prevalent in clinical practice. Konstas et al[38] investigated the efficacy of a fixed combination of bimatoprost and timolol, which they found was able to lower the IOP more than latanoprost in a set of 41 patients with exfoliation syndrome or exfoliative glaucoma (18.9 vs 21.2 mm Hg; $P < 0.001$), without causing any additional adverse events.[38]

Realini and colleagues[39] performed a pooled analysis to compare the effects of treatment with a fixed combination of brinzolamide 1%/brimonidine 0.2% and its component medications on 1350 patients. At the 3-month time point, they found that use of the fixed combination resulted in a statistically significant decrease in IOP compared with either agent alone ($P < 0.0001$). In addition, they found that the safety profile is consistent with that of its individual components.[39] This study included data from Katz and colleagues,[40] who demonstrated similar findings.

In order to investigate the effects of glaucoma therapy on the ocular surface, Lee and colleagues[41] performed a single-center prospective case-control study including 49 normal control subjects, 50 glaucoma patients on chronic preserved antiglaucoma medications (≥6 months), and 31 posttrabeculectomy patients. They found that both subsets of glaucoma patients had an elevated tear film osmolarity (ORs, 4.43 and 2.76 for medically treated and posttrabeculectomy patients, respectively) and were also more likely to experience dry eye symptoms (ORs, 4.72 and 4.24). However, there was no difference between the tear breakup time and Schirmer testing between all 3 groups.[41]

As such, Costa et al[42] performed a retrospective analysis including 175 glaucoma patients and showed that the use of artificial tears was higher in those using more than 2 medications (OR, 1.92) and on treatment for more than 5 years (OR, 2.93) ($P < 0.05$).

Other groups focused on the use of nutritional supplements to ameliorate the signs and symptoms of medication-associated dry eye. Galbis-Estrada et al[43] found that treatment with antioxidants and essential polyunsaturated fatty acids improved ocular surface desiccation in patients with POAG on chronic treatment with ocular hypertensives. Similarly, Nebbioso and colleagues[44] found that treatment with supplements containing a combination of forskolin, rutin, and vitamins B_1 and B_2 helped restore the normal equilibrium of the tear film and improve the symptoms of dry eye.

Given some of these issues with current glaucoma medications, there has been a growing movement toward the development and use of preservative-free formulations. In comparing between 2 formulations of bimatoprost 0.03%, Day and colleagues[45] performed a double-masked parallel-group study on 597 patients and found that preservative-free bimatoprost met all noninferiority criteria over the course of 12 weeks when compared with bimatoprost 0.03% ophthalmic solution.

Recent studies have shown that the chronic use of prostaglandin analogs induces changes to orbital and periocular tissues. To examine these changes further, Shah and colleagues[46] performed a prospective cross-sectional study involving 157 current and 15 former patients on treatment with prostaglandin analogs. These patients were compared with 171 control subjects. Using masked examiners to grade external photographs, they found that current users of prostaglandin analogs exhibited a 230-fold increased risk of incremental involution of dermatochalasis (OR, 2.30; 95% CI, 1.43–3.69; $P = 5.44 \times 10^{-4}$) and a 249-fold increased risk of incremental loss of lower lid steatoblepharon (OR, 2.49; 95% CI, 1.54–4.03; $P = 1.98 \times 10^{-4}$). In addition, upper lid ptosis (OR, 4.04; 95% CI, 2.43 Y6.72; $P = 7.37 \times 10^{-8}$), levator dysfunction (OR, 7.51; 95% CI, 3.39–16.65; $P = 6.74 \times 10^{-7}$), and lower lid retraction (OR, 2.60; 95% CI, 1.58–4.28; $P = 1.72 \times 10^{-4}$) were also associated with the use of these agents.[46]

Giannico et al[47] examined the effects of different topical prostaglandin analogs on eyelash length by applying daily drops onto the left eye of New Zealand white rabbits for 4 weeks. They found that while bimatoprost and tafluprost induced significant increases in eyelash length, there was no significant eyelash growth in rabbits receiving travoprost and latanoprost.[47]

Amid growing evidence highlighting the contribution of ocular lymphatics to aqueous humor outflow, Tam and colleagues[48] performed quantum dot injections into living mouse eyes treated with latanoprost and found that the lymphatic drainage rate into the submandibular lymph node was significantly higher than in control (1.23 ± 1.06 vs 0.30 ± 0.17 per hour; $P < 0.02$).

NEUROPROTECTION

Given that glaucoma progression can occur despite IOP lowering, there remains a definite need for additional therapy. The development of neuroprotective agents has been a strong area of focus over the last decade, as summarized by recent review articles.[49,50] Particular attention has been drawn to the role of neurotrophic molecules that promote neuron survival

and differentiation, cell-based therapies to replace RGCs, the role of immune modulation, and vascular factors such as ocular blood flow.

Recent studies have demonstrated additional mechanisms of action for established IOP lowering medical therapies. Dai and colleagues[51] used a fluorescent mouse model to show that repeated treatment with brimonidine (an α-2 adrenergic receptor agonist) after crush injury imparts neuroprotective effects on RGCs. To investigate the mechanistic pathways, Fujita et al[52] utilized a mouse model to find that brimonidine promotes regeneration of the optic nerve by inducing Erk1/2 phosphorylation following crush injury. Lee et al[53] demonstrated that systemic brimonidine protects RGCs in a rat model of transient ischemia induced by acute IOP elevation by blockade of glutamate excitotoxicity-induced oxidative stress.

Interest in the roles of taurine, erythropoietin, and tumor necrosis factor α (TNF-α) has resurfaced this year. Taurine supplementation in nutrition was found to promote RGC survival in 2 glaucomatous animal models (DBA/2J mice and rats with vein occlusion) and prevent *N*-methyl-D-aspartate–induced RGC excitotoxicity.[54,55] Erythropoietin was shown to impart neuroprotective effects to cultured adult rat RGCs, protecting them against damage induced by TNF-α as well as N-methyl-D-aspartate and trophic factor withdrawal.[56,57] A recent meta-analysis suggested that patients with open-angle glaucoma may have higher TNF-α levels in the aqueous humor and a greater prevalence of specific TNF-α gene polymorphisms compared with control subjects—however, further studies are needed to confirm these results.[58]

There is increasing evidence to support the involvement of autoimmune reactions in glaucoma pathogenesis. Bell et al[59] described the proinflammatory environment found in human glaucomatous retinae, as reflected by the presence of antibody deposits. They concluded that while autoantibodies may not be directly responsible for the manifestations of glaucoma, they could serve as vital diagnostic markers in detecting the disease.[59]

Drug delivery is a key area of focus for glaucoma therapy. The role of nanoparticles and nanovesicles in the delivery of drugs and neurotrophic factors was discussed in a review article by Zarbin et al,[60] which also addressed the potential of nanotechnology in regenerative medicine and artificial vision. Recent attention has also been drawn to the use of stem cell–based gene delivery systems. Subretinal stem cell–based delivery of the brain-derived neurotrophic factor gene to the rat retina using rat bone marrow mesenchymal stem cells has been shown to significantly increase the expression of brain-derived neurotrophic factor for up to 4 weeks following transplantation in axotomized rat retinae.[61] In another study, transplantation of retinal stem cells and vaccination with a glatiramer acetate copolymer-1 were found to protect RGCs from apoptosis in a rat glaucoma model created by performing argon laser photo-coagulation on the episcleral veins and limbal plexus to induce IOP elevation.[62]

Despite promising preclinical studies, there are a number of challenges to establishing neuroprotective agents for use in the clinical arena. In a review article by Liu and Pang,[63] the authors discuss neuroprotective drug discovery and its current limitations, including

unclear therapeutic targets, the lack of animal models that correlate with human glaucoma, and the limitations of clinical end points in glaucoma trials. However, strong collaborations between scientists, clinicians, industry, and governmental bodies have left us well poised for the introduction of adjuvant neuroprotective glaucoma therapies in the future.

GLAUCOMA LASER THERAPY

Lee et al[64] examined 84 eyes of 52 primary angle-closure suspects and found that the angle opening distance, trabecular-iris space area, angle recess area, and trabecular-iris angle all significantly increased following laser peripheral iridotomy. Lower baseline measurements were associated with greater postoperative opening in the parameters assessed.[64]

Desgroseilliers and colleagues[65] found that among patients who had undergone laser peripheral iridotomy, those with positive prone dark-room provocative testing had significantly more synechial angle closure of 180 degrees or more (35% vs 0%; $P = 0.008$) and more frequent double-hump sign (59% vs 11%; $P = 0.005$), reflecting an anteriorly positioned ciliary body. They therefore concluded that dark-room provocative testing may help identify patients at higher risk of intermittent increases in IOP.[65]

Wang and colleagues[66] performed a meta-analysis comparing the efficacy and tolerability of selective laser trabeculoplasty (SLT) and argon laser trabeculoplasty. In their study, which compiled the results from 6 randomized controlled trials, they found that SLT produced a larger reduction in IOP (weighted mean difference [WMD], 0.60; 95% CI, 0.06–1.14), and patients treated with SLT required fewer glaucoma medications following treatment (WMD, 0.29; 95% CI, 0.01–0.56). In addition, they also found that SLT was more effective in lowering IOP in patients who had previously failed laser treatment (WMD, 1.48; 95% CI, 0.75–2.21). There was no statistically significant difference between postprocedure anterior chamber flare and IOP peak with SLT and argon laser trabeculoplasty.[66]

SECONDARY GLAUCOMA

Friedman and colleagues[67] performed a randomized partially masked trial composed of patients with noninfectious uveitis who received treatment with either fluocinolone acetonide implants or systemic therapy. Sixty-five percent of the patients assigned to implants experienced an IOP elevation of 10 mm Hg or greater compared with 24% assigned to systemic treatment ($P < 0.001$). As such, 69% of patients in the implant group required IOP-lowering medication, compared with 26% in the systemic group ($P < 0.001$). Glaucomatous optic nerve damage developed in 23% versus 6% of implant and systemic patients, respectively ($P < 0.001$).[67] Given the risk of IOP elevation and glaucoma development in uveitis patients receiving implants compared with those treated systemically, these findings support the need for aggressive IOP monitoring and early treatment in this population of patients.

GLACUOMA SURGERY: TRABECULECTOMY

Liang et al[68] compiled a group of 176 patients with PACG who underwent trabeculectomy in order to assess the daytime fluctuation of IOP. They found that the mean daytime IOP

was 13.2 ± 3.7 mm Hg, mean peak IOP 15.1 ± 4.1 mm Hg, mean trough IOP 11.3 ± 3.5 mm Hg, and mean fluctuation 3.8 ± 2.1 mm Hg. Fluctuation was positively correlated with peak ($r = 0.528$, $R^2 = 0.28$; $P < 0.001$) and mean IOP ($r = 0.278$, $R^2 = 0.08$; $P < 0.001$), but not with trough IOP ($r = 0.015$; $P = 0.843$). Fluctuation was lower with larger blebs (0.6–mm Hg/U increase in extent; 95% CI, 0.1–1.2 mm Hg) and in blebs with microcysts (1.1–mm Hg less fluctuation; 95% CI, 0.2–1.9 mm Hg).[68]

In order to compare the effects of primary trabeculectomy using either adjunctive subconjunctival bevacizumab or mitomycin C (MMC), Akkan and Cilsim[69] amassed a cohort of 42 patients who were randomized into 2 groups. The mean preoperative IOP in the bevacizumab group improved from 23.9 ± 2.7 mm Hg on 2.6 ± 0.7 antiglaucoma medications to 13.9 ± 2.8 mm Hg on 0.6 ± 0.9 medications at 12 months ($P < 0.001$ and $P < 0.001$). By comparison, the mean preoperative IOP in the MMC group improved from 22.9 ± 2.6 mm Hg on 2.7 ± 0.8 antiglaucoma medications to 12.2 ± 3.2 mm Hg on 0.1 ± 0.5 medications at 12 months ($P < 0.001$ and $P < 0.001$). Furthermore, at the 12-month time point, 15 of 21 eyes in the MMC group met a target IOP of 12 mm Hg off medications, whereas only 7 of 21 eyes in the bevacizumab group met this target ($P = 0.02$).[69]

Following trabeculectomy, Husain and colleagues[70] demonstrated that both anterior chamber depth and axial length decreased by an average of 0.11 and 0.16 mm, respectively. For every 1–mm Hg decrease in IOP, these parameters decreased by 0.02 and 0.01 mm in POAG patients with emmetropia or mild myopia.[70]

Butler et al[71] used a rabbit model to demonstrate that filtration surgery with concurrent topical application of silver nanoparticles led to a reduction in average IOP across all time points and smaller, thicker, and less ischemic blebs compared with rabbits treated with MMC.

GLAUCOMA SURGERY: IMPLANTS

Wang and colleagues[72] performed a meta-analysis to compare the efficacy and tolerability of Ex-PRESS implantation with trabeculectomy in the treatment of patients with uncontrolled glaucoma. Their study, which consisted of 8 controlled trials encompassing 605 eyes of 559 patients, found that the WMD of percentage of IOP reduction from baseline was 2.33 (95% CI, −2.59 to 7.24) when comparing Ex-PRESS with trabeculectomy. The pooled OR was 0.93 (95% CI, 0.39–2.23) for complete success rate and 1.00 (95% CI, 0.39–2.56) for qualified success rate. Furthermore, Ex-PRESS was associated with lower rates of hypotony and hyphema than trabeculectomy.[72]

Kugu and colleagues[73] performed a retrospective analysis of 73 patients who underwent Ahmed glaucoma valve implantation using either the long scleral tunnel technique or the processed pericardial patch graft method and found that the incidence of tube exposure was lower with the former (2.5% vs 7.9%; $P = 0.042$) over the course of follow-up (95% CI, 43.6–46.7 months).

Koh and colleagues[74] performed a retrospective review including 24 eyes of 24 patients with refractory glaucoma who underwent FP8 Ahmed glaucoma valve implantation (surface

area, 96 mm^2) and 76 eyes of 76 patients who underwent FP9 implantation (surface area, 184 mm^2). While patients in the FP8 group exhibited better visual acuity in the early postoperative period, there was no significant difference between vision, IOP reduction, number of medications, or complication rates between the groups over the 3-year follow-up period.[74]

Tai et al[75] performed a retrospective chart review on 45 eyes of 45 patients with preexisting glaucoma who underwent Ahmed glaucoma valve implantation either before or after 1 month following penetrating keratoplasty. Postoperatively, there was no significant difference between groups with respect to graft survival ($P = 0.98$). However, 1 year following surgery, the success rates of IOP control were 80% and 46.7% when patients were treated before and after 1 month, respectively—these rates decreased to 70% and 37.3% at 2 years.[75]

Weiner and colleagues[76] described their experiences with ciliary sulcus–implanted Baerveldt glaucoma tube shunts entirely concealed behind the iris in undilated pseudophakic eyes (n = 15 eyes) in comparison to those with openings fully exposed in the pupillary area (n = 41 eyes). Preoperative IOPs in the concealed and nonconcealed groups were 27.2 ± 9.6 and 25.5 ± 10.6 mm Hg, respectively—these values reduced to 13.3 ± 4.1 and 10.8 ± 4.4 mm Hg following surgery. Similarly, the number of IOP-lowering medications went from 3.9 ± 0.7 and 4.0 ± 1.0 in the 2 groups to 1.9 ± 1.2 and 1.8 ± 1.4. There was no significant difference between groups before ($P = 0.6$) or after surgery ($P = 0.8$). A single case of tube incarceration by the iris was reported in the concealed tube group, although this was treated successfully with laser iridotomy without recurrence.[76]

Paschalis et al[77] described a novel implantable glaucoma valve based on ferrofluidic nanoparticles capable of acting as a pressure-sensitive barrier to aqueous flow. They demonstrated that this model acted in a proportional and reproducible manner over the course of 3 months.

MINIMALLY INVASIVE GLAUCOMA SURGERY

Bahler and colleagues[78] used 7 enucleated human eyes to demonstrate that insertion of an iStent inject increased outflow facility from 0.16 ± 0.05 μL/min per mm Hg to 0.38 ± 0.23 μL/min per mm Hg ($P < 0.03$), with concurrent pressure reduction from 16.7 ± 5.4 mm Hg to 8.6 ± 4.4 mm Hg. Of note, placement of a second iStent inject device further increased outflow to 0.78 ± 0.66 μL/min per mm Hg.[78] Similarly, placement of the Hydrus microstent into the Schlemm canal has also been shown to significantly increase outflow facility in human eyes.[79,80]

Arriola-Villalobos et al[81] performed a prospective, uncontrolled, nonrandomized case series study on 19 patients (mean age, 74.6 ± 8.44 years) with mild or moderate open-angle glaucoma and cataract who underwent phacoemulsification with intraocular lens implantation and iStent placement. At the end of the follow-up period (mean, 53.68 ± 9.26 months), mean IOP was reduced from 19.42 ± 1.89 mm Hg to 16.26 ± 4.23 mm Hg ($P = 0.002$), and the mean number of pressure-lowering medications decreased from 1.32 ± 0.48 to 0.84 ± 0.89 ($P = 0.046$). In addition, mean best corrected visual acuity improved from

0.29 ± 0.13 to 0.62 ± 0.3 ($P < 0.001$).[81] Hoeh et al[82] reported successful results placing the suprachoroidal Cypass microstent in conjunction with cataract surgery in a case series consisting of 184 patients with controlled (IOP G21 mm Hg) and uncontrolled (IOP Q21 mm Hg) open-angle glaucoma. Intraocular pressure–controlled patients (n = 41) had a 71.4% reduction in glaucoma medication ($P < 0.001$), whereas those with uncontrolled pressure (n = 57) had a 37% reduction in IOP ($P < 0.001$) with a 50% reduction in glaucoma medications at 6 months ($P < 0.001$).[82]

Matlach and colleagues[83] compared the results of patients with concomitant cataract and glaucoma undergoing phacotrabeculectomy versus phacocanaloplasty. Over a 12-month follow-up period, baseline IOP decreased from 30.0 ± 5.3 mm Hg with an average of 2.5 ± 1.2 glaucoma medications to 11.7 ± 3.5 mm Hg with a mean of 0.2 ± 0.4 medications in eyes with phacotrabeculectomy ($P < 0.0001$). Eyes with phacocanaloplasty had a preoperative IOP of 28.3 ± 4.1 mm Hg on 2.8 ± 1.1 pressure-lowering drops. At 12 months, IOP decreased to 12.6 ± 2.1 mm Hg on 1.0 ± 1.5 topical medications ($P < 0.05$).[83]

CONCLUSIONS

The studies outlined above represent only a small sampling of the glaucoma research conducted over the past year. They touch upon many different concepts carried out in both the clinical and basic science settings, reflecting the expansive scope of glaucoma research. Although these studies represent great progress in understanding the multiple facets of glaucoma and optimizing the diagnosis and treatment of patients, they also raise many new questions that will undoubtedly serve as the impetus, which drives the field in the years to come.

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