Literature review

https://doi.org/10.31288/oftalmolzh202423239

Current strategy of treatment for neovascular glaucoma secondary to retinal ischemic lesions

O.V. Guzun, O.S. Zadorozhnyy, Chargui Wael

SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine";

Odesa (Ukraine)

Keywords:

neovascular glaucoma, secondary glaucoma, absolute glaucoma, intraocular pressure, neovascularization of the angle, rubeosis iridis

The paper considers current views on the treatment of patients with neovascular glaucoma. Numerous treatments (ocular hypotensive medications, laser and surgical techniques and their combinations) have been attempted for intraocular pressure (IOP) control in NVG, but no consensus exists regarding the most effective medication or procedure. NVG requires emergency eye care, and its treatment is focused mostly on combating neovascularization and stabilizing the IOP. An advanced standardized multidisciplinary strategy for the management of patients with NVG is warranted to improve treatment outcomes for these patients. In patients with NVG, it is reasonable to use treatments aimed at (1) compensating for the underlying disease, (2) reducing retinal ischemia and neovascularization (such as panretinal laser photocoagulation and/or anti-vascular endothelial growth factor (VEGF) therapy) and (3) lowering an abruptly elevated IOP (such as topical and systemic medical treatment and surgical and cyclodestructive procedures).

Introduction

Neovascular glaucoma (NVG) is a devastating and potentially blinding disease that is often refractory to medical and/or surgical therapies. Numerous treatments have been attempted for intraocular pressure (IOP) control in NVG, but no consensus exists regarding specific treatment [1].

NVG is a disease that occurs secondary to mostly pathological conditions that cause retinal ischemia. The two most common etiologies for NVG are proliferative diabetic retinopathy (PDR) and retinal vein occlusion (RVO) [2]. The third most common etiology is ocular ischemic syndrome (OIS) which is often caused by ipsilateral carotid artery stenosis leading to decreased ocular perfusion [3]. Retinal ischemia triggers a release of angiogenic factors that promote neovascularization of the iris and of the angle, leading to persistently elevated IOP [4].

Given that the prognosis for patients with NVG is poor, and their quality of life is severely affected, a methodological and comprehensive approach to treatment is needed. A variety of therapeutic strategies for NVG are reported, but their therapeutic effects are not ideal. Clinical practice has demonstrated the importance of the following basic principles:

- Systemic treatment should be focused on the control of the underlying disease.

- Ocular treatment should be focused on the control of IOP, ocular pain and inflammation; reduction in the release of proangiogenic factors (anti-VEGF therapy); and anti-ischemic measures (preliminary anterior panretinal laser photocoagulation (PRP)).

1. Systemic treatment

Compensation for the underlying disease (diabetic mellitus (DM), hypertensive heart disease, carotid artery obstruction, etc.) as well as normalization of the fibrinolytic activity of plasma is essential in the management of NVG.

Tang and colleagues [5] reviewed the development of risk factors and cytokines in retinal vein occlusion (RVO) and noted that a cardiovascular disease and thrombotic factors are major risk factors of RVO. Central venous occlusion increases hydrostatic resistance, which results in blood flow stagnation and retinal ischemia injury, this leading to the upregulation of VEGF and the development of neovasculatization. Cytokines act as powerful mediators of pathological conditions, such as inflammation, neovascularization (IL-8) and macular edema [5].

The relationship between hyperglycemia and diabetic retinopathy is well known. Perais and colleagues [6]

searched the Cochrane Central Register of Controlled Trials and conducted meta-analyses to review other risk factors for the development and progression of diabetic retinopathy. They concluded that increased HbA1c is likely to be associated with progression to PDR. Renal impairment in people with T1DM or T2DM, as well as younger age at diagnosis of DM, increased triglyceride levels and increased retinal venular diameters in people with T1DM may also be associated with increased risk of progression to PDR.

Early control of oxidative stress is imperative in patients with DM. Oxidative stress causes metabolic derangements and the accumulation of toxic products, DNA damage in the nucleus and mitochondria, and alterations in signaling pathways controlling reactive oxygen species (ROS) production. Sufficiently advanced, such damage likely renders oxidative stress self-sustaining. Cell apoptosis and dysfunction as a result of these mechanisms is proposed to cause the clinical features of DR like neurodegeneration, vascular leakage and vessel degeneration, retinal ischemia and edema [7].

Early treatment of the underlying disease reduces retinal ischemia, thus preventing the development of NVG in the fellow eye in patients with unilateral NVG [4]. Improved blood glucose control may prevent the progression of DR to PDR. Patients with a kidney disease may have a higher risk of progressing to PDR. Therefore, it is not surprise that that rates for NVG are substantially lower (as low as 8%) in patients who receives intensive treatment of the underlying disease in combination with eye treatment (including PRP) compared to those who receives conventional treatment of the underlying disease [4, 8].

Treatment of patients with secondary glaucoma requires a meticulous diagnostic and therapeutic approach, often involving a multidisciplinary team of specialists in glaucoma, endocrinology and cardiology, to achieve adequate control of IOP, blood pressure, retinal ischemia, blood glucose, lipids, and inflammatory blood factors [9]. Unfortunately, even after underlying disease is compensated, patients with NVG may experience abruptly elevated IOP and severe eye pain, report poor quality of life and have poor visual prognosis. Therefore, there is a need for additional methods of treatment for NVG.

2. Management of ocular changes

2.1. Ocular hypotensive medication therapy

Ocular hypotensive medications which inhibit the secretion of intraocular fluid by ciliary epithelial cells are indicated for the reduction of elevated IOP and improved patient comfort. These include oral and topical carboanhydrase inhibitors, beta blockers and alpha-2 agonists which increase uveoscleral outflow. Prostaglandin analogs may increase inflammation and macular edema, which should be avoided in patients with preserved visual function [10]. Hyperosmotic agents (mannitol and glycerol) can be used as a temporizing measure in emergency.

2.2. Anti-inflammatory therapy

Increasing evidence points to inflammation as a key factor in the pathogenesis of NVG. The progression of neovascularization in patients with NVG involves not only vascular endothelial growth factors, but also inflammatory mediators. Chronic low-grade inflammation in the retina is a key driver of capillary occlusion and hypoxia that reinforces VEGF expression and concomitant vascular abnormalities of PDR, RVO and OIS. Several processes (e.g., oxidative stress, ischemia, and hyperglycemia) contribute to the inflammatory process in these conditions [11].

The role of inflammation in the pathogenesis of NVG has been confirmed by numerous studies. Patients with DR have higher levels of inflammatory cytokines in the vitreous than normals. The activation of CD40 receptor in Müller cells induces low-grade inflammation and vascular changes (leukostasis and capillary lesions) in diabetic retina [12]. Significant differences were found between patients with NVG and healthy controls with regard to the levels of white blood cells (WBC) and neutrophils, neutrophil-to-lymphocyte ratio and lymphocyte-to-monocyte ratio [13]. Based on the findings of Liu and colleagues [14], there is subset of microglia associated with neovascularization during pathological retinal angiogenesis. A reduction in inflammation and microglial activation attenuates aberrant retinal angiogenesis in oxygen-induced retinopathy rats [15]. RVO initiates an inflammatory response whereby resident microglia cells are activated. They trigger infiltration of neutrophils that exacerbate blood-retina barrier damage, regulate postischemic inflammation and irreversible loss of neuroretina. Suppression of microglia-mediated inflammation might bear potential for combating neovascularization [16]. In addition, inflammation contributes to retinal neurodegeneration in patients with DR [17]. We have reported previously [18] on reduced levels of the molecular marker of intracellular adhesion (ICAM-1) in patients with NVG after transscleral laser cyclocoagulation.

Therefore, inflammation plays a key role in the pathogenesis of NVG, which indicates the need for anti-inflammatory therapy in patients with the disease [19]. Aggressive inflammation control is essential for treatment success and preservation of vision. Steroids are administered topically and orally to reduce fibrin formation, inflammation, vascular permeability and edema [20]. Aggressive control of inflammation is critical to prevent complications of cyclophotocoagulation laser. Khodeiry and colleagues [20] typically apply sub-tenons triamcinolone (for long slow-release steroid), sub-conjunctival decadron, and aggressive topical prednisolone and ketorolac for 3–4 weeks. In some cases, they also use oral prednisone to control intraocular inflammation, especially in patients with a known history of auto-immune or uveitic disease. The taper of steroids is also very slow at a minimum of one drop less every 2–3 weeks in conjunction with ketorolac.

2.3 Anti-VEGF therapy

Anti-VEGF agents are specific inhibitors of primary neovascularization mediators. Aflibercept, bevacizumab, ranibizumab, pegaptanib and brolucizumab can inhibit VEGF expression and, therefore, prevent neovascularization. There have been reports on the efficacy of these medications in controlling IOP in neovascular glaucoma [21, 22].

Anti-VEGF injections lead to the regression of neovascularization not only in the retina, but also in the iris and angle in the presence of an incomplete fibrovascular membrane. The effects of anti-VEGF agents for treating NVG, however, are temporary, generally lasting four to six weeks [22].

Simha and colleagues (2020) [22] reviewed numerous studies on the use of intravitreal anti-VEGF injections in NVG; it was, however, impossible to evaluate this data quantitatively due to their significant clinical, methodological and statistical heterogeneity. Rittiphairoj and colleagues (2023) [23] reviewed randomized controlled trials on anti-VEGF therapy for the treatment of NVG and concluded that anti-VEGFs as an adjuct to conventional treatment could help reduce IOP in NVG in the short term (four to six weeks), but there was no evidence that this is likely in the longer term. There was very low certainty of evidence on the long-term safety and efficacy of anti-VEGFs in improving visual acuity and achieving complete regression of new iris vessels in NVG [23].

A prospective, randomized, double-masked, sham-controlled study found that early treatment with intravitreal anti-VEGF therapy decreases the rates of anterior segment neovascularization and NVG after CRVO [24].

The European Glaucoma Society Guidelines (2021) recommend using intravitreal anti-VEGF injections before or after NVG surgery to prevent intraoperative or postoperative complications [22]. Li and colleagues (2023) [25] concluded that the comprehensive treatment of pars plana vitrectomy (PPV), endoscopic PRP, and endoscopic cyclophotocoagulation (CPC) surgery for NVG patients after anti-VEGF injection can control IOP effectively and be friendly to patients' BCVA without obvious serious complications throughout a 12-months follow-up period.

In addition to having potent vasopermeability and some angiogenic activity, VEGF is an important neurovasculotrophic factor that is critical to the survival and function of neurons and endothelial cells. Because neurovascular cell functions are already compromised by underlying disease, potent, long-lasting VEGF antagonism may be detrimental to the health of cells dependent on its trophic activity. Patients with ischemic (e.g., diabetes, ARMD) retinopathies are likely to have ischemia elsewhere (e.g., heart, brain, kidneys), and the sustained presence of potent VEGF antagonists may prevent adequate collateralization and function in these tissues as well. Consequently, repeat anti-VEGF injections may precipitate problems from suppressed VEGF activity in high-risk patients like those with diabetes and cardiovascular disorders [26].

Therefore, short-lasting anti-VEGF therapy may be used as a component of multicomponent therapy for NVG in case of incomplete fibrovascular blockade of the anterior chamber angle, but currently evidence is limited on the long-term safety and efficacy of anti-VEGF agents in NVG.

2.4. Surgical treatment for NVG

NVG is a refractory form of secondary glaucoma in which adequate IOP control is difficult to achieve with medical management alone. Although the risk of postoperative complications is high, about 50% of eyes with NVG require surgical stabilization of the IOP [27].

Surgery is required in patients with NVG refractory to maximal medical therapy and showing a fibrovascular membrane in the angle of the anterior chamber, which hampers the aqueous outflow. In addition, surgery is performed in the presence of optimistic visual prognosis. This includes trabeculectomy in combination with antimetabolites and implantation of drainage devices.

Choy and colleagues (2018) [28] reported on complications of the Ahmed glaucoma valve (AGV) in the management of NVG. Hyphema was the most common complication; other complications included intraoperative bleeding, corneal decompensation, overfiltration, implant exposure, cataract progression and phthisis bulbi. Both the Ex-PRESS glaucoma filtration device and transscleral cyclophotocoagulation (TSCPC) might constitute safe and alternative therapeutic tools for patients with NVG. However, TSCPC is an easier procedure, less time consuming, and does not require a learning curve [29].

Compared to trabeculectomy alone, trabeculectomy combined with intravitreal anti-VEGF injections for the treatment of NVG had a lower risk of postoperative complications, a higher success rate and a significantly greater IOP reduction at 1 week to 6 months after surgery [30].

The probability of success of trabeculectomy with mitomycin C (MMC) for NVG 1 year after surgery ranged from 62.6% to 81.2%, and 5 years after surgery was 51.3% [2, 31, 32].

Hyphema was the most common complication of this surgery, too. Compared to CRVO and OIS, the eyes with NVG secondary to PDR had poor success with trabeculectomy [2].

Shchomak and colleagues (2019) [33] conducted a meta-analysis to compare IOP lowering efficacy, failure rates and loss of light perception (LP) rates 6 months after an IOP-lowering surgical procedure in NVG eyes. They concluded that there appears to be no difference in IOP-lowering efficacy between glaucoma drainage devices (GDDs) and cyclophotocoagulation, although GDDs appear to be safer. AGV and trabeculectomy also seem to provide similar IOP-lowering results with trabeculectomy showing lower failure rates.

Others compared four methods of management of NVG in diabetic eyes (Trabeculectomy with MMC; AGV; Ex-Press Minishunt with MMC; and Diode CPC) in terms of the outcome. At 1 year, there was no significant dif-

ference between the groups for IOP and BCVA, but CPC showed the lowest incidence of intraoperative bleeding [34].

Lin and colleagues (2022) [35] reviewed randomised controlled trials and cohort studies involving 1303 patients to compare the short-term effectiveness and safety of the six interventions for NVG. In the treatment of NVG, AGV+intravitreal anti-VEGF therapy and cyclophotocoagulation were more effective in terms of IOP reduction and success rate than the other four interventions [35].

Therefore, trabeculectomy with MMC (or implantation of glaucoma drainage devices) combined with adequate control of neovascularization (via anti-VEGF therapy) is the effective option for IOP control in NVG.

2.5. Panretinal laser photocoagulation

PRP is believed to be an effective treatment of angle neovascularization in patients with NVG. PRP aims at reducing ischemia in the eye and restoring homeostatic balance between proangiogenic factors at all stages of the disease. Ohnishi and colleagues repoted following panretinal photocoagulation in 26 of the patients with NVG, angle neovascularisation remarkably regressed in 12 and moderately regressed in 7 patients [36].

If a diabetic patient develops NVG in one eye, there is a relatively high risk of NVG development in the fellow eye without prophylactic PRP [4].

Therefore, the prompt and intensive management of diabetes is of great importance. A study with longterm observation of 9 years reported that the rates for NVG were 24% in diabetic patients who received conventional treatment, and 8% for those who received intensive treatment [8], indicating that the management does make a difference in the prognosis of the refractory disease.

Increased IOP in OIS is often refractory to medical therapy. PRP should be done prior to surgery if the view is clear; this will lead to regression of iris vascularisation in 36% of cases and control of IOP if angles are still open [37]. In patients with open-angle NVG secondary to OIS, serial monthly anti-VEGF injections may be necessary combined with PRP to suppress underlying neovascular drive and regress anterior segment neovascularization, maintain physiologic IOP, and prevent synechial angle closure [3].

PRP should be performed as soon as possible in patients with NVG. Because PRP does not result immediately in regression of neovascularizarion, but results in a longer treatment effect than anti-VEGF therapy, it is feasible to combine these two methods of treatment. PRP is indicated not only in initial rubeosis, but also in late stages of NVG with goniosynechiae. In eyes with high IOP where the media are not clear enough to perform PRP in a transpupillary fashion, PRP should be performed after cataract extraction or intraoperatively during vitrectomy.

2.6. Cyclodestructive treatment

In patients with NVG, adequate IOP control is difficult to achieve with medical management alone, whereas adequate intraoperative IOP control is associated with an increased risk of postoperative complications such as hyphema and vision loss. This is why cyclodestruction is an essential component in the treatment of NVG. Cyclodestructive procedures are often performed as a treatment of last resort in NVG patients with extremely elevated IOP and marked eye pain. These procedures lower pressure by producing necrosis of ciliary secretory cells which causes reduced aqueous secretion. Cyclodestructive procedures are associated with lower rates of postoperative complications and are more eye-sparing approaches than conventional NVG surgery (e.g. aqueous shunt implantation), which is reflected in indications for treatment of NVG [10].

2.6.1. Cyclocryotherapy

Cyclocryotherapy (CCT) refers to the trans-scleral application of a cryo-probe over the ciliary processes with the aim of ablating sufficient ciliary tissue so that aqueous humor inflow (and hence IOP) is reduced to clinically acceptable levels. Typically, rapid freezing to temperatures around - 70 ºC results in the formation of intracellular micro-crystals that eventually leads to destruction of ciliary secretory cells. Cryoablation also leads to small vessel obliteration and necrosis of the ciliary body in addition to the destruction of ciliary epithelial cells [38].

An undesirable collateral effect of CCT, however, may be the damage inflicted upon the neighboring trabecular meshwork due to the extension of the cryoablated area. This trabecular outflow damage may lead to the procedure losing its effect over time. Another, mostly desirable, collateral effect of cyclocryotherapy is the reduction of corneal sensitivity due to the damage of corneal nerves; this may allow some patients with painful eyes to experience less pain, despite the IOP remaining high.

Benson and Nelson [39] reviewed the case notes of all patients undergoing CCT at a single centre over a 10-year period. Of those eyes which were painful preoperatively 71.4% were comfortable, but 30% of patients lost their vision following the procedure. In a study by Ruixue and colleagues (2020) [40], after six months of follow-up, the IOP value decreased to 30.4 ± 9.1mmHg, 73% of patients had no eye pain, and complications occurred in all cases, for those treated by CCT. In addition, the number of patients with no light perception increased from 9 to 18 after surgery. Histological findings after CCT included atrophy and loss of integrity of ciliary processes. Some epithelial cells separated from the ciliary body in a balloon-like manner. With necrosis of the epithelial cells, the stroma of the ciliary process was also affected, resulting in hyperemia and edema. In addition, a large number of inflammatory cells infiltrated the ciliary body, causing capillary rupture and microbleeding [40].

It is likely that the risk of complications is associated with the impossibility of the strict control of ciliary body temperature during freezing; scleral thickness, cryo-probe location and surgical technique may affect the possibility of this control. Large contact areas of the cryoprobe may also induce the range that is larger than desired and cause

excessive destruction by freezing the ciliary body and collateral tissues resulting in reactive inflammation and destruction of the vascular system of the ciliary body [38].

CCE and diode laser CPC are equally effective in decreasing IOP in patients with persistent uncontrolled glaucoma, with a lower rate of complications associated with diode laser CPC [41].

Clinical and experimental studies indicate that, compared to CPC, CCT is less safe and comfortable for patients with NVG [42].

2.6.2. Cyclophotocoagulation

In patients with NVG, diode laser CPC is used for more focused, controlled and selective ciliary body coagulation, compared to diathermy and cryotherapy, thereby minimizing the impact upon adjacent structures [43]. CPC methods may be classified based on the type of laser and approach to the ciliary body (transscleral, endoscopic, transpupillary and transvitreal approaches). Li and colleagues (2023) [25] concluded that the comprehensive treatment of PPV, endoscopic PRP, and endoscopic CPC surgery for NVG patients after anti-VEGF injection can control IOP effectively and be friendly to patients' BCVA without obvious serious complications throughout a 12-months follow-up period.

TSCPC has been extensively used to lower elevated IOP in secondary NVG. The 1064-nm Nd-YAG laser and 810-nm diode laser are used in TSCPC. The latter affords selective absorption of its wavelength by the uveal melanin and deeper ciliary body coagulation. The mechanism of therapeutic effect of CPC consists in a reduced aqueous production by the ciliary body. A transscleral approach to cyclophotocoagulation is believed to be safe and efficacious, with an IOP lower than 22 mmHg achieved in 68-99.4% of patients with refractory glaucoma [44].

Diode lasers have been widely used transsclerally in NVG, with high rates of successful IOP control. Compared to CCT, TSCPC has lower complication rates and is less aggressive [42].

Complications after TSCPC include inflammation, corneal edema, hyphema, vitreous hemorrhage, increased IOP or hypotony, ocular subatrophy, and phthisis bulbi. Isolated complications (conjunctival burns and sleral perforation) during TSCPC have been reported [45].

Given a current tendency to perform diode laser CPC in patients with good visual acuity, it is important to reduce the risk of complications in this category of patients [46].

Choy and colleagues (2018) [28] compared the effectiveness and safety of diode laser TSCPC with the AGV in the management of NVG. The success rate was 63% for TSCPC and 42% for AGV, and eyes with AGV implant tended to have higher rates of visual loss and complications. Wagdy and Zaky [29] compared the outcomes of Ex-PRESS glaucoma filtration device and TSCPC in the management of NVG, and a complete success in lowering IOP was observed in 50% and 44.44% of eyes, respectively. A meta-analysis by Shchomak and colleagues (2019) [33] concluded that there appeared to be no difference in IOP-lowering efficacy and loss of light perception rates in eyes with NVG between glaucoma drainage devices and CPC. Shalaby and colleagues (2022) [47] aimed to determine the outcomes of AGV and transscleral diode CPC in NVG, and found that AGV and CPC had comparable IOP and medication reduction in NVG eyes at 6 months. A difference in surgical failure between the continuous wave-CPC and micropulse-CPC groups was not detected [47]. In a Ford and colleagues' pilot study (2022) [48] assessing treatment outcomes in NVG using AMG with and without CPC, a significantly lower IOP was seen in the former group compared to the latter group at 3 and 6 months.

Delgado and colleagues [42] used Nd:YAG CPC in NVG and demonstrated a probability of continued success (defined as an IOP </=22 mmHg) at 1 year of 65.0%, at 3 years of 49.8%, and at 6 years of 34.8%. Impulse laser energy of 2.5-4.5 J is believed to be necessary for effective diode laser TSCPC of the ciliary body.

The accurate localization of cliary body structures during TSCPC is challenging [49, 50]. Targeted TSCPC of the ciliary body in patients with NVG enables an effective reduction in IOP with a reduction in the amount of laser energy delivered during a treatment session and, consequently, a reduction in the risk of complications [50].

Brancato and colleagues (1991) [51] investigated the impact of diode laser on enucleated rabbit eyes at 24 hours after a cyclodestructive procedure, whereas in a study by McKelvie and Walland (2002) [52], the time to enucleation of human eyes ranged from 2 weeks to 4 years after diode laser cyclophotocoagulation. The major histopathological findings in rabbit eyes at 24 hours after CPC included epithelial and stromal coagulative necrosis of the pars plicata and vascular stasis and thrombosis [53]. This is in agreement with loss of ciliary processes with pigment clumping and loss of vessels in enucleated human eyes at later time points after diode laser cyclophotocoagulation [52].

Previously, we have investigated histological changes in the intraocular structures of an enucleated eye with uveal melanoma and secondary painful neovascular glaucoma after palliative diode TSCPC. We found significantly less damage to the intraocular structures with the presence of treatment effect (reduction in IOP and eye pain) [54] compared to the findings reported by Moussa et al (2020) [55].

An 810-nm diode laser TSCPC with laser settings of 1,000 mW and 1.5 s duration was found to lead to the destruction of ciliary processes in the form of disorganization and focal coagulative necrosis of the pigment epithelium [54]. Continuous wave (CW) and micropulse (MP) laser modes have been extensively used for TSCPC. In patients with refractory glaucoma, the combination of augmented MP-TSCPC with limited CW-TSCPC provided a significant IOP-lowering effect and decrease in medication burden without increased risk of postoperative complications [56].

Khodeiry and colleagues [19] reported treatment outcomes of slow-coagulation CW-TSCPC (1250-milliwatt power and 4-second duration) as an initial surgical in-

tervention in patients with NVG. The cumulative probabilities of success at 12 and 24 months were 71.7% and 64.2%, respectively. The most common complications were decrease in baseline VA (13.2%) and anterior chamber inflammation (9.4%).

Diode CPC decreases IOP more effectively than cyclocryocoagulation in children with secondary glaucoma [57].

Therefore, we believe that, compared to conventional filtration surgeries, AGV surgeries and cyclocryocoagulation, non-invasive TSCPC has substantial advantages in terms of safety and efficacy profiles.

Conclusion

NVG, a progressive secondary glaucoma, can be challenging to treat, typically results in severe vision loss, and can result even in anatomical loss of the eye. The onset of elevated IOP is often acute and painful, and exacerbated by associated anterior-chamber hemorrhage and inflammation. This requires urgent intervention, especially, in the presence of visual acuity of 0.01 or better.

An advanced standardized multidisciplinary strategy for the management of patients with NVG is warranted to improve treatment outcomes for these patients. An early diagnosis and an interdisciplinary approach are important for the preservation of visual functions in patients with glaucoma. Treatment of NVG is focused mostly on combating neovascularization and stabilizing the IOP. An early and adequate treatment of the underlying cause of ischemia and IOP control are keys to effective treatment of the condition. NVG treatment should be aimed at preserving visual functions as much as possible as well as improving the quality of life.

Compensation for the underlying disease and ocular hypotensive and anti-inflammatory medications are components of management of patients with NVG. Anti-VEGF therapy can be used as a component of management for NVG with an incomplete fibrovascular membrane in the angle of the anterior chamber, with subsequent PRP, which is still the gold standard treatment for neovascularization in the presence of clear optical media. In patients with advanced NVG, it is reasonable to use treatments (such as PRP and/or anti-VEGF therapy) aimed at reducing retinal ischemia and neovascularization and lowering an abruptly elevated IOP (such as topical and systemic medical treatment and surgical and cyclodestructive procedures). Since, compared to other types of treatment for NVG, CPC has substantial advantages in terms of efficacy and long-term safety, it is reasonable to recommend it as a component in the strategy of treatment for patients with NVG. There are, however, still problems in the long-term treatment of NVG, which warrant further investigation and the search for improved treatment options (e.g., prospects for modification of TSCPC).

References

1. **Ramji S, Nagi G, Ansari AS, Kailani O.** A systematic review and meta-analysis of randomised controlled trials in the management of neovascular glaucoma: absence of consensus and variability in practice. Graefes Arch Clin Exp Ophthalmol. 2023;261(2):477-501.
2. **Senthil S, Chary R, Ali MH, Cherukuri JR, Rani PK, Krishnamurthy R, et al.** Trabeculectomy for neovascular glaucoma in proliferative diabetic retinopathy, central retinal vein occlusion, and ocular ischemic syndrome: Surgical outcomes and prognostic factors for failure. Indian J Ophthalmol. 2021;69(11):3341-8.
3. **Asif H, Si Z, Quan S, Amin P, Dao D, Shaw L, et al.** Neovascular Glaucoma from Ocular Ischemic Syndrome Treated with Serial Monthly Intravitreal Bevacizumab and Panretinal Photocoagulation: A Case Report. Case Rep Ophthalmol Med. 2022;2022:4959522.
4. **Havens SJ, Gulati V.** Neovascular glaucoma. Dev Ophthalmol. 2016;55:196–204.
5. **Tang Y, Cheng Y, Wang S, Wang Y, Liu P, Wu H.** Review: The Development of Risk Factors and Cytokines in Retinal Vein Occlusion. Front Med (Lausanne). 2022 Jun 15;9:910600.
6. **Perais J, Agarwal R, Evans JR, Loveman E, Colquitt JL, Owens D,** Prognostic factors for the development and progression of proliferative diabetic retinopathy in people with diabetic retinopathy. Cochrane Database Syst Rev. 2023;2:CD013775.
7. **Haydinger CD, Oliver GF, Ashander LM, Smith JR.** Oxidative Stress and Its Regulation in Diabetic Retinopathy. Antioxidants (Basel). 2023;12(8):1649.
8. Progression of retinopathy with intensive versus conventional treatment in the diabetes control and complications trial. Diabetes control and complications trial research group. Ophthalmology. 1995;102(4):647–61.
9. **Łazicka-Gałecka M, Guszkowska M, Gałecki T, Dziedziak J, Kamińska A, Szaflik J.** Epidemiology, pathophysiology and diagnosis of uveitic glaucoma and ocular hypertension secondary to uveitis. Klinika Oczna / Acta Ophthalmologica Polonica. 2023;125(1):7-12.
10. European Glaucoma Society Terminology and Guidelines for Glaucoma, 5th Edition. Br J Ophthalmol. 2021;105(Suppl 1):1-169.
11. **Tang Y, Shi Y, Fan Z.** The mechanism and therapeutic strategies for neovascular glaucoma secondary to diabetic retinopathy. Front Endocrinol (Lausanne). 2023;14:1102361. doi:10.3389/fendo.2023.1102361.
12. **Abcouwer SF.** Müller cell-microglia cross talk drives neuroinflammation in diabetic retinopathy. Diabetes. 2017;66(2):261-263.
13. **Zhang A, Ning L, Han J, Ma Y, Ma Y, Cao W, et al.** Neutrophil-to-lymphocyte ratio as a potential biomarker of neovascular glaucoma. Ocul Immunol Inflammation. 2021;29(2):417–24.
14. **Liu Z, Shi H, Xu J, Yang Q, Ma Q, Mao X, et al.** Single-cell transcriptome analyses reveal microglia types associated with proliferative retinopathy. JCI Insight 2022;7:e160940.
15. **Wang JH, Lin FL, Chen J, Zhu L, Chuang YF, Tu L, et al.** TAK1 blockade as a therapy for retinal neovascularization. Pharmacol Res. 2023;187:106617.
16. **Fu X, Feng S, Qin H, Yan L, Zheng C, Yao K.** Microglia: The breakthrough to treat neovascularization and repair

blood-retinal barrier in retinopathy. Front Mol Neurosci. 2023;23;16:1100254.
17. **Wang W, Lo ACY.** Diabetic retinopathy: pathophysiology and treatments. Int J Mol Sci. 2018; 19(6):1816.
18. **Guzun OV, Velichko LN, Bogdanova AV, Zadorozhnyy OS, Korol AR.** Dynamics of the molecular marker of intercellular adhesion (ICAM-1) in patients with neovascular glaucoma after transscleral laser cyclocoagulation. 10-th World glaucoma congress. June 28-July 1, 2023, Rome, Italy. Abstract book. PLB-013 - P.431.
19. **Khodeiry MM, Lauter AJ, Sayed MS, Han Y, Lee RK.** Primary slow-coagulation transscleral cyclophotocoagulation laser treatment for medically recalcitrant neovascular glaucoma. Br J Ophthalmol. 2023;107(5):671-676.
20. **Khodeiry MM, Liu X, Lee RK.** Clinical outcomes of slow-coagulation continuous-wave transscleral cyclophotocoagulation laser for treatment of glaucoma. Curr Opin Ophthalmol. 2022;33(3):237-242.
21. **Palfi Salavat MC, Șeclăman EP, Barac R, Ungureanu E, Iorgu G, Artamonov A, et al.** The role of Anti-VEGF agents in treatment of neovascular glaucoma. Rom J Ophthalmol. 2022;66(3):209-213. doi:10.22336/rjo.2022.41
22. **Simha A, Aziz K, Braganza A, Abraham L, Samuel P, Lindsley KB.** Anti-vascular endothelial growth factor for neovascular glaucoma. Cochrane Database Syst Rev. 2020;2(2):CD007920. doi: 10.1002/14651858.CD007920.pub3.
23. **Rittiphairoj T, Roberti G, Michelessi M**. Anti-vascular endothelial growth factor for neovascular glaucoma. Cochrane Database Syst Rev. 2023;4(4):CD007920. doi: 10.1002/14651858.CD007920.pub4.
24. **Lucatto LFA, Magalhães-Junior O, Prazeres JMB, Ferreira AM, Oliveira RA, Moraes NS, et a**l. Incidence of anterior segment neovascularization during intravitreal treatment for macular edema secondary to central retinal vein occlusion. Arq Bras Oftalmol. 2017;80(2):97-103.
25. **Li J, Zhang S, Hou B.** Outcomes of vitrectomy, complete pan-retinal photocoagulation, and endoscopic cyclophotocoagulation surgery after anti-VEGF treatment in neovascular glaucoma. Adv Ophthalmol Pract Res. 2023;3(3):112-118.
26. **Usui-Ouchi A, Friedlander M.** Anti-VEGF therapy: higher potency and long-lasting antagonism are not necessarily better. J Clin Invest. 2019;129(8):3032-3034.
27. **Rani PK, Sen P, Sahoo NK, Senthil S, et al**. Outcomes of neovascular glaucoma in eyes presenting with moderate to good visual potential. Int Ophthalmol. 2021;41:2359–68.
28. **Choy B, Lai J, Yeung J, Chan J.** Randomized comparative trial of diode laser transscleral cyclophotocoagulation versus Ahmed glaucoma valve for neovascular glaucoma in Chinese - a pilot study. Clin Ophthalmol. 2018;12:2545–2552.
29. **Wagdy FM, Zaky AG.** Comparison between the express implant and transscleral diode laser in neovascular glaucoma. J Ophthalmol. 2020;107:1–6.
30. **Zhou X, Chen J, Luo W, Du Y.** Short-Term Outcomes of Trabeculectomy With or Without Anti-VEGF in Patients With Neovascular Glaucoma: A Systematic Review and Meta-Analysis. Transl Vis Sci Technol. 2023;12(9):12.
31. **Takihara Y, Inatani M, Fukushima M, Iwao K, Iwao M, Tanihara H**. Trabeculectomy with mitomycin-C for neovascular glaucoma: Prognostic factors for surgical failure. Am J Ophthalmol. 2009;147:912–8. e911.
32. **Higashide T, Ohkubo S, Sugiyama K.** Long-term outcomes and prognostic factors of trabeculectomy following intraocular bevacizumab injection for neovascular glaucoma. PLoS One. 2015;10:e0135766. doi: 10.1371/journal.pone.0135766.
33. **Shchomak Z, Cordeiro Sousa D, Leal I, Abegão Pinto L.** Surgical treatment of neovascular glaucoma: a systematic review and meta-analysis. Graefes Arch Clin Exp Ophthalmol. 2019;257(6):1079-1089.
34. **El-Saied HMA, Abdelhakim MASE.** Various modalities for management of secondary angle closure neovascular glaucoma in diabetic eyes: 1-year comparative study. Int Ophthalmol. 2021;41(4):1179-1190.
35. **Lin P, Zhao Q, He J, Fan W, He W, Lai M.** Comparisons of the short-term effectiveness and safety of surgical treatment for neovascular glaucoma: a systematic review and network meta-analysis. BMJ Open. 2022;12(5):e051794.
36. **Ohnishi Y, Ishibashi T, Sagawa T.** Fluorescein gonioangiography in diabetic neovascularization. Graefes Arch. Clin. Exp. Ophthalmol. 1994; 232:199-204.
37. **Sood G, Siddik AB.** Ocular Ischemic Syndrome. In: StatPearls. Treasure Island (FL): StatPearls Publishing; August 13, 2023.
38. **Zadorozhnyy OS, Savin NV, Buiko AS**. Improving the technique for controlled cryogenic destruction of conjunctival tumors located in the projection of the ciliary body onto the sclera: A preliminary report. J Ophthalmol (Ukraine). 2018;5:60-65. https://doi.org/10.31288/oftalmolzh201856065
39. **Benson MT, Nelson ME.** Cyclocryotherapy: a review of cases over a 10-year period. Br J Ophthalmol. 1990;74(2):103-5.
40. Ruixue W, Tao W, Ning L. A Comparative Study between Ultrasound Cycloplasty and Cyclocryotherapy for the Treatment of Neovascular Glaucoma. J Ophthalmol. 2020;2020:4016536.
41. **Goldenberg-Cohen N, Bahar I, Ostashinski M, Lusky M, Weinberger D, Gaton DD.** Cyclocryotherapy versus transscleral diode laser cyclophotocoagulation for uncontrolled intraocular pressure. Ophthalmic Surg Lasers Imaging. 2005;36(4):272-9.
42. **Delgado MF, Dickens CJ, Iwach AG, Novack GD, Nychka DS, Wong PC, et al.** Long-term results of noncontact neodymium:yttrium-aluminum-garnet cyclophotocoagulation in neovascular glaucoma. Ophthalmology. 2003;110(5):895–899.
43. **Denis P, Aptel F, Rouland JF, Nordmann JP, Lachkar Y, Renard JP, et al.** Cyclocoagulation of the ciliary bodies by high-intensity focused ultrasound: a 12-month multicenter study. Invest Ophthalmol Vis Sci. 2015;56(2):1089–1096.
44. **Dastiridou AI, Katsanos A, Denis P, Francis BA, Mikropoulos DG, Teus MA, et al.** Cyclodestructive Procedures in Glaucoma: A Review of Current and Emerging Options. Adv Ther. 2018;35(12):2103-2127.
45. **Billings B, Fletcher DB, Weaver AC, Alkaelani MT, Fallgatter K, Daneshvar R.** Scleral burn and perforation following transscleral cyclophotocoagulation. Am J Ophthalmol Case Rep. 2023;32:101893.
46. **Rotchford AP, Jayasawal R, Madhusudhan S, Ho S, King AJ, Vernon SA.** Transscleral diode laser cycloablation in patients with good vision. Br J Ophthalmol. 2010;94(9):1180-1183.
47. **Shalaby WS, Ganjei AY, Wogu B, Myers JS, Moster MR, Razeghinejad R, et al.** Outcomes of Ahmed glaucoma valve and transscleral cyclophotocoagulation in neovascular glaucoma. Indian J Ophthalmol. 2022;70(4):1253-1259.

48. **Ford RL, Knight OJ, Klifto MR, Zhang AY, Wiesen CA, Fleischman D**. A Pilot Study Assessing Treatment Outcomes in Neovascular Glaucoma Using Ahmed Glaucoma Valve with and without Cyclophotocoagulation. J Curr Glaucoma Pract. 2022;16(1):4-10.
49. **Zadorozhnyy O, Alibet Y, Kryvoruchko A, Levytska G, Pasyechnikova N.** Dimensions of ciliary body structures in various axial lengths in patients with rhegmatogenous retinal detachment. J Ophthalmol (Ukraine). 2017;6:32-35. https://doi.org/10.31288/oftalmolzh201763236
50. **Zadorozhnyy O, Guzun O, Kustryn T, Nasinnyk I, Chechin P, Korol A.** Targeted transscleral laser photocoagulation of the ciliary body in patients with neovascular glaucoma. J Ophthalmol (Ukraine). 2019;4:3–7. https://doi.org/10.31288/ oftalmolzh2019437.
51. **Brancato R., Leoni G., Trabucchi G., Cappellini A.** Histopathology of continuous wave neodymium:yttrium aluminum garnet and diode laser contact transscleral lesions in rabbit ciliary body. A comparative study. Invest Ophthalmol Vis Sci. 2004;32:1586–92.
52. **McKelvie PA, Walland MJ.** Pathology of cyclodiode laser: a series of nine enucleated eyes. Br J Ophthalmol. 2002;86(4):381–386.
53. **Chechyn PP, Vyt VV, Huzun OV.** Histomorphological changes in the sclera and ciliary body after transscleral contact-compression neodymium laser coagulation. J Ophthalmol (Ukraine). 2018;2:41-44. in Russian.
54. **Guzun O, Zadorozhnyy O, Artyomov A, Elagina V.** Histological Changes in the Intraocular Structures of an Enucleated Eye with Uveal Melanoma and Secondary Painful Neovascular Glaucoma after Palliative Diode Transscleral Cyclophotocoagulation (Clinical Case). Oftalmologija. Vostochnaja Evropa. 2021;3(11):368-377.
55. **Moussa K, Feinstein M, Pekmezci M.** Histologic Changes Following Continuous Wave and Micropulse Transscleral Cyclophotocoagulation: A Randomized Comparative Study. Transl Vis Sci Technol. 2020;9(5):22.
56. **Gupta S, Chang EK, Chachanidze M, Hall N, Neeson C, Klug E, et al**. Outcomes of a combination of augmented MicroPulse and limited Continuous Wave Cyclophotocoagulation in patients with refractory glaucoma. Graefes Arch Clin Exp Ophthalmol. 2022;260(5):1583-1592.
57. **Koraszewska-Matuszewska B, Leszczyński R, Samochowiec-Donocik E, Nawrocka L**. Cyclodestructive procedures in secondary glaucoma in children. Klin Oczna. 2004;106(1-2 Suppl):199-200.

Disclosures

Received 19.12.2023
Accepted 29.01.2024

Corresponding author: *Olga V. Guzun, E-mail: olga.v.guzun@gmail.com*

Author Contributions: *Conceptualization and study design: OG; Literature data curation and analysis: OG, OZ, ChV; Writing – original draft preparation: OG. All authors reviewed the results and approved the final version of the manuscript.*

This paper is a part of the research program by the Filatov Institute of Eye Diseases and Tissue Therapy (registration number № 0122U001490).

Disclaimer: *The opinions presented in this article are those of the authors and do not necessary represent those of their institutions.*

Conflict of interest: *All authors declare no conflict of interest that could influence their views on the subject matter or materials described and discussed in this manuscript.*

Funding sources: *No external funding sources were used for this study.*

Abbreviations: *CCT – cyclocryotherapy; CPC – cyclophotocoagulation; DM – diabetes mellitus; DR – diabetic retinopathy; IOP – intraocular pressure; NVG – neovascular glaucoma; OIS – ocular ischemic syndrome; PDR – proliferative diabetic retinopathy; PRP – panretinal laser photocoagulation; RVO – retinal vein occlusion; TSCPC – transscleral cyclophotocoagulation; VA – visual acuity*

.