Trends in neovascular glaucoma management: Practice patterns of glaucoma and retina specialists in the United States

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INTRODUCTION

Neovascular glaucoma (NVG) is a condition that arises from neovascularization (NV) of the anterior surface of the iris and iridocorneal angle causing obstruction of aqueous humor outflow, usually secondary to posterior segment ischemic or vaso-occlusive processes. The greatest percentage of cases result from retinal venous occlusion, followed by diabetic retinopathy, carotid artery occlusive disease, central retinal artery occlusion, rhegmatogenous retinal detachment, and inflammatory or neoplastic causes.¹¹ This condition warrants a multifaceted therapeutic approach that includes both temporizing and permanent measures for successful management.
Multiple approaches to the management of NVG exist, generally with the goal of prevention of visual loss and pain relief. However, balancing IOP management and the underlying ischemic process often requires a multi-disciplinary approach to decrease the ischemic drive, achieve a normal IOP, and avoid optic nerve damage. However there is inconclusive evidence to support a “best practice” approach to NVG. Traditionally, pan-retinal photocoagulation (PRP), IOP-lowering topical agents, and surgical IOP management have been long-time treatment options for NVG.[2,3] With the advent of anti-VEGF agents, there have been numerous studies to determine its role in the management of NVG.[4–8] However, to determine an optimal combination of these therapies in the setting of NVG, input from a multi-disciplinary standpoint may lead to further consensus and guidelines. The purpose of this survey study was to identify similarities and differences in NVG management between and within glaucoma and retina specialists.

MATERIALS AND METHODS/SUBJECTS

This study was submitted to the Clevel and Clinic Foundation Institutional Review Board (IRB), and was considered exempt research as no identifiable patient information was utilized. An 8-question survey was drafted in concert by a medical retina specialist, surgical retina specialist, and a glaucoma specialist. Questions posed as vignettes were based on actual clinical cases presenting to our institution between June 2014 and June 2016. Survey questions were multiple-choice format and answer banks were developed with the intention of deter-mining therapeutic preferences amongst retina and glaucoma specialists, and included initial therapy and next best-step clinical vignettes based on actual cases of NVG that described the vision, intraocular pressure, and prior procedures for each patient [Table 1]. Further, support for each clinical vignette answer bank was based on previous descriptions of therapeutic approaches to the management of NVG in the literature through comparative studies and randomized clinical trials (RCTs). The survey was open for 6 weeks between June and July of 2016. The web-based anonymous survey (administered using Survey Monkey”) was posted on the American Glaucoma Society (AGS) Listserv to 1200 members, and on the American Society of Retinal Specialists (ASRS) Listserv to 1676 members. The response rate varied per question, with a range of 195–235 responses overall. Statistical significance was determined using the Chi-Square test.

RESULTS

A total of 109 of 1200 glaucoma specialists (9%) and 130 of 1676 retina specialists (7.8%) initiated the survey (239 total participants). There was an 81.6% completion rate for all participants. Among glaucoma specialists, there was a 64% completion rate, and among retina specialists the completion rate was 95%. Table 1 displays the survey questions, and Table 2 displays the complete results of the survey by question for all participants, and subdivided categories reporting results for the glaucoma and retina specialist groups.

Initial treatment of NVG in the setting of good visual acuity

The results of Question 2 [Figure 1A] address initial management of NVG in a patient with 20/50 visual acuity (VA) and IOP of 37 following PRP, and reveal that 52.3% (67/128) of retina specialists preferred anti-VEGF alone, versus 18.1% (17/94) of glaucoma specialists (P < 0.01). Preference for anti-VEGF therapy combined with anterior chamber tube shunt was 32.8% (42/128) and 71.28% (67/94) of retinal and glaucoma specialists, respectively (P < 0.01).
Question 5 describes a patient presenting with VA measuring 20/80 and NVG with IOP of 44, and revealed a similar response breakdown [Figure 1b]. Anti-VEGF therapy as first-line treatment was chosen by 92.7% (115/124) of retina specialists; 40.8% (31/76) of glaucoma specialists also chose anti-VEGF as first-line treatment with their second most common response being referral to a retina specialist in 39.5% (30/76). PRP was recommended as first-line therapy by 5.7% (7/124) and 1.3% (1/76) of retina and glaucoma specialists, respectively. A tube shunt procedure (anterior or posterior) was recommended as first-line therapy by 15.8% (12/76) of glaucoma specialists, and 1.6% (2/124) of retina specialists (P < 0.01).

Table 2: Survey Results.

<table>
<thead>
<tr>
<th>Answer Options</th>
<th>Retina Responses</th>
<th>Glaucoma Responses</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-VEGF alone</td>
<td>67/128 (52%)</td>
<td>15/64 (23.8%)</td>
<td>0.193</td>
</tr>
<tr>
<td>Anti-VEGF + AC tube shunt</td>
<td>42/128 (33.8%)</td>
<td>15/32 (46.8%)</td>
<td>0.128</td>
</tr>
<tr>
<td>Tube shunt</td>
<td>8/125 (6.4%)</td>
<td>14/32 (43.7%)</td>
<td>0.044</td>
</tr>
<tr>
<td>TSCPC</td>
<td>1/125 (0.8%)</td>
<td>0/32 (0%)</td>
<td></td>
</tr>
<tr>
<td>Continued anti-VEGF</td>
<td>12/125 (9.6%)</td>
<td>0/32 (0%)</td>
<td></td>
</tr>
<tr>
<td>Anti-VEGF alone + PRP</td>
<td>114/126 (90.48%)</td>
<td>31/32 (96.9%)</td>
<td>0.211</td>
</tr>
<tr>
<td>PRP</td>
<td>9/126 (7.1%)</td>
<td>3/32 (9.4%)</td>
<td>0.462</td>
</tr>
<tr>
<td>TSCPC</td>
<td>0/126 (0%)</td>
<td>0/32 (0%)</td>
<td></td>
</tr>
<tr>
<td>Anti-VEGF + AC tube shunt</td>
<td>115/124 (92.9%)</td>
<td>31/32 (96.9%)</td>
<td>0.381</td>
</tr>
<tr>
<td>Tube shunt</td>
<td>2/124 (1.6%)</td>
<td>12/32 (37.5%)</td>
<td>0.188</td>
</tr>
<tr>
<td>PRP</td>
<td>116/124 (93.0%)</td>
<td>52/32 (81.3%)</td>
<td>0.601</td>
</tr>
<tr>
<td>Tube shunt</td>
<td>7/124 (5.7%)</td>
<td>22/32 (68.8%)</td>
<td>0.451</td>
</tr>
<tr>
<td>No further anti-VEGF</td>
<td>62/124 (50%)</td>
<td>34/32 (106.8%)</td>
<td>0.966</td>
</tr>
<tr>
<td>anti-VEGF for at least 3 months</td>
<td>45/124 (36.3%)</td>
<td>22/32 (68.8%)</td>
<td>0.594</td>
</tr>
<tr>
<td>anti-VEGF for at least 6 months</td>
<td>13/124 (10.5%)</td>
<td>11/32 (34.4%)</td>
<td>0.403</td>
</tr>
<tr>
<td>Combo therapy</td>
<td>28/124 (22.6%)</td>
<td>15/32 (46.9%)</td>
<td>0.302</td>
</tr>
<tr>
<td>Glaucoma surgery + combo therapy</td>
<td>11/124 (8.9%)</td>
<td>17/32 (53.1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>anti-VEGF + PRP</td>
<td>40/124 (32.3%)</td>
<td>11/32 (34.4%)</td>
<td>0.111</td>
</tr>
</tbody>
</table>

AC = anterior chamber, TSCPC = transscleral cyclophotocoagulation; PRP = panretinal photocoagulation.

Figure 1: Graph representing the distribution of responses from glaucoma and retina specialists to two questions describing clinical vignettes regarding initial treatment in the setting of good visual acuity. A. Responses to question 2. B Responses to question 5. Bolded percentages represent statistically significant differences. PPV – pars plana vitrectomy; TSCPC – transscleral cyclophotocoagulation; PRP – panretinal photocoagulation.

Initial treatment in the setting of poor visual acuity

The overall consensus for the initial management of acute NVG [Figure 2A] with IOP of 42 in the setting of chronic counting fingers (CF) vision and a microhyphema (Question 4) was for the use of anti-VEGF agents, chosen by 90.5% (114/126) of retina specialists; 38.3% (31/81) of glaucoma specialists also chose anti-VEGF as first-line therapy in addition to 40.7% (33/81) of glaucoma specialists first choice being referral to a retina specialist for first line management. Only 7.1% (9/126) of retinal specialists would initially treat this condition with panretinal photocoagulation (PRP) versus 3.7% (3/81) of glaucoma specialists; this difference was not statistically significant (P = 0.4662).

Question 8 addressed the acute management of NVG with IOP elevated to 32 in a patient with chronic HM vision due to a central retinal artery occlusion [Figure 2B]. In this case, both groups favored combination therapy including the use of anti-VEGF agents, PRP, and IOP lowering medications; 47.3% (35/74) and 38.71% (48/124) of glaucoma and retina respondents, respectively, chose this approach (P = 0.3002). However, differences were noted in the decision to include IOP lowering surgical procedures including TSCPC, trabeculectomy, and tube shunt in addition to the previously listed three therapies. All four of the listed therapies were chosen by 24.3% (18/74) of glaucoma specialists and 8.9% (11/124) of retinal specialists (P < 0.01). Lastly, 32.3% (40/124) of retina specialists favored the use of only anti-VEGF agents and PRP versus 14.86% (11/74) of glaucoma respondents (P < 0.01).

Next best step in therapeutic management

Question 6 presented a scenario of normalized IOP in a patient with 20/80 VA following the administration of a single dose of an anti-VEGF agent combined with the use of oral and topical IOP lowering medications [Figure 3A]. The next best step in management was considered PPV in 93.6% (116/124) of retinal respondents and 68.4% (52/76) of glau-
coma respondents (P < 0.01). Tube shunt procedures (anterior or posterior) were favored by 29.0% (22/76) of glaucoma specialists and 5.7% (7/124) of retina specialists (P < 0.01) as the next best step in management.

Question 3 addressed the management of a patient with NVG that has undergone anti-VEGF therapy and full PRP, but has persistently elevated IOP above 30 and finger counting VA [Figure 3B]. Similar responses were noted for both glaucoma and retinal specialists. A tube shunt procedure was favored by 53.9% (48/89) of glaucoma specialists and 64.8% (81/125) of retinal specialists (P = 0.1444). TSCPC was the second choice for treatment with 41.6% (37/89) of glaucoma specialists and 23.2% (29/125) of retinal specialists choosing this as the next best step in management (P < 0.01).

Following adequate management of NVG and IOP stabilization (Question 7; Figure 3C), 50.0% (62/124) of retina respondents and 48.6% (62/124) of retina respondents felt continued anti-VEGF therapy was not merited (P = 0.9668), while 36.3% (45/124) of retina respondents and 31.4% (22/70) of glaucoma respondents recommended continuation for at least 3 months following stabilization (P = 0.5984). These numbers decreased further to 10.5% (13/124) and 15.7% (11/70) for retinal and glaucoma respondents favoring continuing anti-VEGF therapy for at least 6 months following initial treatment and stabilization (P = 0.4034).

DISCUSSION

NVG is a potentially blinding complication of retinal-vascular disease with a high rate of severe vision loss to hand movement or light perception in many cases. Recent studies have demonstrated that anti-VEGF therapy is non-inferior to PRP, and further that anti-VEGF therapy may halt the progression of diabetic retinopathy and even improve diabetic retinopathy severity scores. Therefore, the use of anti-VEGF agents as first-line for treatment of proliferative diabetic retinopathy (PDR) is increasing, and raising concerns for a resultant increase in poorly compliant patients to return with progression of disease and vision threatening complications such as NVG. This has been noted in a recent study by Wubben and
colleagues where 5/12 PDR patients treated with anti-VEGF therapy alone as first-line therapy were lost to follow-up and had developed NVG on the return visit.[13]

This survey was developed for gaining insight into practice patterns for the management or co-management of NVG in the real-world setting. The findings of this survey demonstrate the importance of anti-VEGF agents in the management of NVG. In every scenario of initial management of NVG, the majority of both glaucoma and retina practitioners favor a therapeutic option that includes anti-VEGF therapy. In an RCT in 2009 by Yazdani and colleagues, 26 eyes received conventional treatment for NVG. Fourteen eyes were randomly selected to undergo intravitreal bevacizumab (IVB) injections at 4-week intervals, and 12 eyes underwent sham injections. The IVB group demonstrated significant reductions in IOP and NVI from baseline at 1, 3, and 6 months after intervention; however, the sham eyes remained unchanged or increased in both areas of NVI and IOP.[14] This early study demonstrated the role for anti-VEGF as an adjunctive therapy to conventional treatment for NVG which has maintained as a part of initial management of NVG. In our survey, Question 7 addressed the practice of continuing anti-VEGF therapy for 3 months following initial stabilization of IOP, similar to the practice described by Yazdani and colleagues, however this support was by only one-third of all respondents without statistical significance between retina and glaucoma specialists.

Various publications have investigated the role of anti-VEGF as pre-treatment or adjunctive treatment to PRP in NVG management, this practice is addressed in Questions 6 and 8. A mainstay of therapy, PRP, has demonstrated its ability to cause regression of iris NV and IOP reduction alone.[15] A study in 2008 by Ehlers et al. investigated the efficacy of anti-VEGF therapy plus PRP, finding a statistically significant difference in rate and frequency of NV regression in the combination group, but no differences in visual acuity outcomes or IOP-lowering effect were seen.[5] Further, a retrospective study by Olmos et al. concluded that PRP was the most important factor reducing the need for glaucoma surgery, and found no long-term differences between those patients who received anti-VEGF versus those who did not.[6]

Regarding anti-VEGF use as an adjunct to IOP-lowering surgery, this study revealed a statistically significant difference between specialist preferences for anti-VEGF therapy alone (retina specialists) versus anti-VEGF combined with tube shunt surgery (glaucoma specialists) in question 2. Multiple studies investigating the role of anti-VEGF as an adjunct therapy to tube shunt procedures exist and are largely inconclusive regarding long-term benefits with respect to VA and surgical outcomes.[7,17,18]

The ability for retina and glaucoma subspecialists to act in concert with one another to determine the sequence of treatments and/or surgical interventions may lead to better outcomes. A study in 2018 reviewed 16 patients who received PRP followed by intravitreal bevacizumab 4-60 days prior to AGV implantation, the failure rate at 63 months (range 24–84) was noted at 50% with 3 eyes requiring additional surgery and 5 eyes progressing to NLP vision.[19] Combination surgery including pars plana vitrectomy (PPV) and IOP lowering surgery may be useful in some NVG patients. A study in 2017 by Wang and colleagues reviewed 33 eyes with NVG and VH who under went IVR treatment 3–7 days prior to PPV + AGV or PPV + trabeculectomy. The AGV group demonstrated success rates of 71.3% versus 46.7% in the trabeculectomy group.[20] A study in 2017 by Sun and colleagues demonstrated high levels of success comparing a combined approach between trabeculectomy or Ahmed glaucoma valve, both with pre-operative intravitreal ranibizumab and post-operative PRP. Success rates were 81.8% and 82.6% respectively regarding lower IOP and improved vision with no significant difference between groups.[21] These studies demonstrate how aggressive management combining anti-VEGF therapy with PRP and IOP lowering surgery, and PPV in some cases, may yield the highest successful outcomes. However, barriers to treatment including access to subspecialists especially in rural or private practice settings can alter preferred timing and order of procedural interventions.

Our results show that IOP lowering surgery is favored significantly in nearly all settings by glaucoma specialists over retina specialists. Questions 2, 5, 6, and 8 all reveal a statistically significant preference for surgical intervention among glaucoma specialists as compared to retina specialists. This may represent a bias of skill set versus a sense thatube shunt is superior in the long-term management of NVG, which has been established in previous studies.[22,23] Further, the role for cyclodestructive procedures is unclear as Question 3 demonstrated TSCPC as the second choice behind tube shunt surgery for treatment by glaucoma specialists. A prospective comparative study assigning 66 patients to diode laser cyclophotoagulation or Ahmed valve implant for IOP control in NVG demon-strated no significant differences in the success rate between the cyclophotoagulation and AGV groups.[24] The nature of cyclodestructive techniques makes them often less predictable and harder to control. This unpredictable dose-effect relation-ship combined with the risk of serious postoperative inflammation reactions complicates the decision to use such procedures in eyes with optimistic visual prognosis and may explain why they were the second procedure of choice in this survey.

**CONCLUSION**

While all of these procedures, or a combination of these procedures, have been shown to be somewhat successful in NVG patients, another potentially more pertinent question
is raised regarding the timing and order of such procedures. As in the study by Sun and colleagues, the strongest rates of success were seen in patients who underwent anti-VEGF therapy 3–7 days prior to IOP lowering surgery followed by PRP. This may be a starting point for a guideline in the development of a patient care pathway, recognizing that presenting VA, opportunity for visual gain, and patient compliance are all confounding factors.

Overall, strengths of this survey study include the relatively well-balanced group of respondents in each specialty, the use of actual case-presentations previously treated at our facility (Cleveland Clinic, Cole Eye Institute), and the distribution of the survey to specialists in all practice settings including, academic, private, and multi-specialty group practices. The anonymous, masked nature of the survey did not allow for answers to be viewed by other participants. The actual number of responses was over 100 in each specialty, and while the percentage responding was not extremely high, we can assume that these clinicians treat a number of NVG cases every year, thus, affecting an overall number of cases that is exponentially higher.

Weaknesses include the limitation of distribution of the survey to only ASRS and AGS members, completion rates less than initiation rates in both groups, but more prevalent amongst glaucoma specialists leading to a potential bias toward the group with higher response rates. The voluntary multiple-choice nature of the survey creates a nonrandom sample and bias toward motivated responders, in addition to limiting response variety and choices through a simplified view of a complex problem. A higher response rate would have added further data, but the 239 participants did provide perspective into management trends.

The results of this survey identify similarities and differences in practice patterns between and within retina and glaucoma specialists, and highlight how NVG is a nuanced problem in practice patterns between and within retina and glaucoma specialists, and influence clinical decision-making. Further studies evaluating the role and timing of interventions including anti-VEGF therapy, PRP, and IOP lowering surgery in the management of this disease are needed, and further position papers might have both groups return for a consensus Delphi panel in addressing NVG for optimization of patient care.

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Conflicts of interest
Dr. Rishi P Singh is on the Editorial Board of the Journal.

REFERENCES


