

# National Survey of the Ophthalmic Use of Anti-Vascular Endothelial Growth Factor Drugs in Israel

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**ABSTRACT:** **Background:** Intravitreal injections of the anti-vascular endothelial growth factor (VEGF) drugs bevacizumab (Avastin®) and ranibizumab (Lucentis®) became the mainstay of treatment for various retinal pathologies, but there is no consensus among ophthalmologists on the precise use of these drugs.

**Objectives:** To describe the routine practices of retinal specialists in Israel regarding anti-VEGF drug treatment.

**Methods:** A questionnaire was sent via email to all 62 members of the Israeli Society of Retinal Specialists. The survey included 34 questions on various aspects of the use of anti-VEGF drugs: diagnosis, treatment, follow-up of different retinal pathologies, and the measures taken for ensuring sterile administration of the intravitreal injections.

**Results:** Fifty members (80%) completed the survey. Most of them (56%) offered both bevacizumab and ranibizumab to their patients for age-related macular degeneration, but 70% were influenced by the patient's socioeconomic status. Three consecutive monthly injections were usually recommended (58%) for the first 3 months, and treatment was extended as long as subretinal or intraretinal fluids persisted (57%). Over two-thirds (68%) switched the drugs after the 3-monthly series if the first one yielded no improvement in fluid status. The routine practice for intravitreal injection (> 80%) involved the wearing of sterile gloves, using an eyelid speculum, and administering povidone-iodine pretreatment and topical antibiotics after treatment.

**Conclusions:** Intravitreal VEGF administration varies widely among Israeli retinal specialists. The current survey is intended to assist Israeli ophthalmologists in establishing their own treatment strategy for patients with retinal pathologies.

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**KEY WORDS:** bevacizumab, ranibizumab, anti-vascular endothelial growth factor, national survey, guidelines

The intravitreal administration of the anti-vascular endothelial growth factor drugs, ranibizumab (Lucentis®, Genentech, San Francisco, CA, USA) and bevacizumab (Avastin®, Genentech), for age-related macular degenera-

VEGF = vascular endothelial growth factor

tion and other retinal pathologies is widely used around the world. While ranibizumab, an anti-VEGF antibody fragment, is the only drug approved by the U.S. Food and Drug Administration for AMD, its relatively high cost encouraged the off-label use of the full-length antibody bevacizumab [1, 2]. Many guidelines have been suggested for the use of these anti-VEGF drugs, but there is still no consensus on this issue among retinal specialists. The American Society of Retinal Specialists conducts a yearly survey in which ophthalmologists are asked their personal opinion and about their experience regarding retina-associated controversies. The main goal of the current study was to reflect the routine practices of Israeli retinal specialists in the use of anti-VEGF drugs vis-à-vis the ASRS Preferences And Trends survey [3].

## SUBJECTS AND METHODS

We conducted a national survey of the 62 members of the Israeli Society of Retinal Specialists via email. The list included 34 questions in the following categories: diagnosis, treatment and follow-up of AMD patients, and measures taken to ensure sterile administration of intravitreal injections of the anti-VEGF drugs for them as well as for patients with diabetic retinopathy, vascular occlusions, neovascular glaucoma and myopic choroidal neovascularization. Two email reminders were followed by a telephone request to complete the survey in order to achieve maximal compliance of the participants.

## RESULTS

Eighty percent of the members of the Israeli Society of Retinal Specialists (50/62) completed the survey, and the leading responses to the items relating to the diagnosis and follow-up of AMD patients are as follows. Two-thirds (67%) of the responding physicians always refer the patient to fluorescein angiography before initiating treatment, while 29% considered clinical examination and optical coherence tomography imaging to be sufficient. Around one-third (34%) referred patients to fluorescein angiography when there had been no

AMD = age-related macular degeneration  
ASRS = American Society of Retinal Specialists

substantial decrease in fluid status and no improvement in visual acuity. Others (23%) relied solely on OCT findings or referred to fluorescein angiography every 3 months (10%) or 6 months (10%), regardless of VA or fluid status on OCT. The first follow-up examination was scheduled at 4–6 weeks (60%), 1 week (24%) and 3 days (8%) after the administration of an anti-VEGF drug. The measures taken for obtaining sterile conditions during intravitreal anti-VEGF injections are listed in Table 1, and the retinal specialists' standard protocols for anti-VEGF administration in AMD in Table 2.

For patients with diabetic retinopathy, 41% of physicians use an anti-VEGF drug after 1–2 failed focal treatments, 20% use an anti-VEGF drug after 3–4 failed focal treatments and 21% prefer triamcinolone acetate (Kenalog®, Bristol-Myers-Squibb, Princeton, NJ, USA). Forty-two percent responded that the patient's lens status (phakic versus pseudophakic) did not affect their decision to treat clinically significant macular edema with triamcinolone acetate, while 40% reserved its use for pseudophakic patients. Fifty-four percent reported administering an anti-VEGF drug for high-risk character-

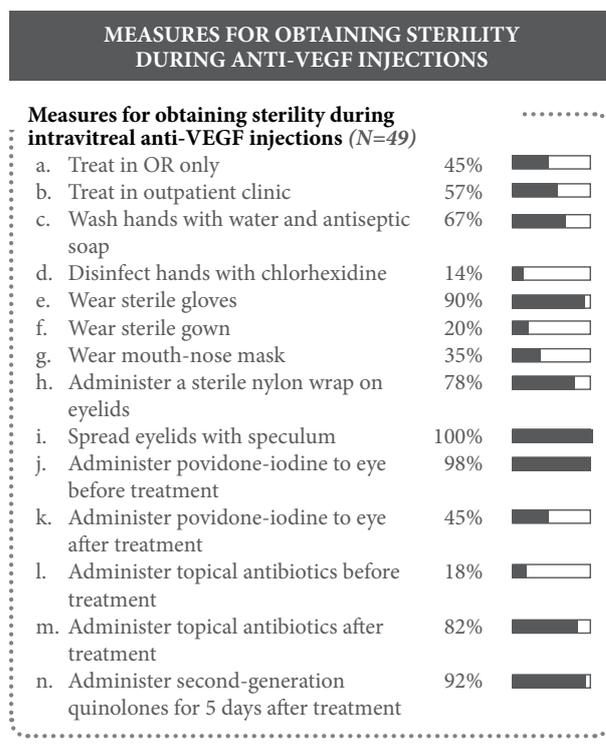
istics proliferative diabetic retinopathy with neovascularization only after completing full panretinal photocoagulation, compared with 8% who would treat before PRP had been completed, while 16% would avoid anti-VEGF treatment in this case altogether.

When queried about treating a hypothetical case involving a 30 year old patient with extensive HRC PDR and severe CSME, the responses were as follows: 31% favored focal treatment followed by PRP and an anti-VEGF drug between treatments (31%), focal treatment followed by PRP only (24%), and focal treatment followed by PRP and then an anti-VEGF drug (18%). For a patient with vitreous hemorrhage and no previous PRP treatment, 40% avoid treatment with an anti-VEGF drug compared with 32% who prescribe one within 1 month.

Preferences of treatment for vascular occlusions, neovascular glaucoma and myopic CNV were as follows: for patients with non-ischemic central retinal vein occlusion, macular edema and VA of 6/15, 60% of the responding physicians treat with an anti-VEGF drug after the appearance of the edema compared with 21% who wait 3 months to treat and do so only if the CRVO or the macular edema does not improve. For a patient with ischemic CRVO, no macular edema and VA > 6/60, 49% treat with an anti-VEGF drug only after the macular edema appears, 21% treat with an anti-VEGF without delay and 15% treat after 3 months if CRVO does not improve. Most physicians (94%) follow patients with non-ischemic CRVO and resolved macular edema (as confirmed by OCT) after three anti-VEGF treatments every 4–6 months, and administer an anti-VEGF drug in the event of recurrence of the macular edema. For treating a patient with perfused branch retinal vein occlusion, VA 6/8.5 and macular edema, 35% recommend follow-up only, 29% perform grid laser and 21% administer an anti-VEGF drug or combined anti-VEGF drug with grid laser treatment. Patients who are post-perfused BRVO, with VA 6/15 and macular edema receive grid laser only (30%), an anti-VEGF drug only (18%), or a combination of both laser and an anti-VEGF drug (40%). Patients with non-arteritic anterior ischemic optic neuropathy, VA 6/60 and an altitudinal visual field defect receive an anti-VEGF drug from only 2% of the responding physicians (83% did not offer this treatment for this condition). Treatment of neovascular glaucoma and elevated intraocular pressure was usually a combination of an anti-VEGF drug and PRP (88%), while far fewer physicians (8%) completed PRP before initiating anti-VEGF treatment. The treatment of choice for myopic CNV was bevacizumab (73%), ranibizumab (11%) and photodynamic therapy (7%).

OCT = optical coherence tomography  
VA = visual acuity

**Table 1.** Results of a national survey describing the steps taken for obtaining sterile conditions during intravitreal anti-VEGF injections among retinal specialists in Israel



OR = operating room  
VEGF = vascular endothelial growth factor

PRP = panretinal photocoagulation  
HRC PDR = high-risk characteristics proliferative diabetic retinopathy  
CSME = clinically significant macular edema  
CNV = choroidal neovascularization  
CRVO = central retinal vein occlusion  
BRVO = branch retinal vein occlusion

**Table 2.** Results of a national survey describing the routine practice of using anti-VEGF drugs for age-related macular degeneration among retinal specialists in Israel

ROUTINE PRACTICE OF USING ANTI-VEGF DRUGS FOR AGE-RELATED MACULAR DEGENERATION	
<b>1. Treatment of choice for CNV (N=50)</b>	
a. Bevacizumab	40%
b. Ranibizumab	4%
c. Offer either bevacizumab or ranibizumab	56%
<b>2. Higher efficacy according to physician's personal experience (N=50)</b>	
a. Bevacizumab	2%
b. Ranibizumab	10%
c. Both have similar efficacy	44%
d. Can not determine	42%
e. Other	2%
<b>3. Influence of the patient's socioeconomic status on the decision to offer bevacizumab or ranibizumab (N=50)</b>	
a. No influence	26%
b. Some influence	22%
c. Moderate influence	18%
d. Strong influence	30%
e. Other	4%
<b>4. Treatment of CNV during the first three months from diagnosis (N=50)</b>	
a. Administer IVT bevacizumab for 3 consecutive months without using OCT, but examine the patient monthly	20%
b. Administer IVT bevacizumab for 3 consecutive months without using OCT and not examining the patient monthly	8%
c. Administer IVT bevacizumab for 3 consecutive months with OCT and examining the patient monthly	30%
d. Perform OCT and examine the patient monthly; decide on treatment accordingly	38%
e. Other	4%
<b>5. Treatment of CNV with anti-VEGF drugs (N=50)</b>	
a. Treat as long as SRF or intraretinal fluid appears on OCT	67%
b. Administer IVT injection after the resolution of fluids on OCT	23%
c. Administer monthly IVT injections for at least 1 year regardless of OCT findings	0%
d. Other	10%
<b>6. Treatment of PED with SRF and intra-retinal fluids (N=50)</b>	
a. Treat until the SRF resolves, regardless of the PED status	57%
b. Treat until both SRF and PED resolve	39%
c. Treat every 4-6 weeks regardless of the SRF or PED status	0%
d. Other	4%
<b>7. Switch from bevacizumab to ranibizumab (N=50)</b>	
a. Always use bevacizumab	18%
b. Switch after ≥3 injections without fluid status improvement	69%
c. Switch after ≥3 injections without VA improvement	2%
d. Other	11%
<b>8. Switch from ranibizumab to bevacizumab (N=46)</b>	
a. Always use ranibizumab	13%
b. Switch after 3 injections or more without fluid status improvement	68%
c. Switch after 3 injections or more without VA improvement	4%
d. Other	15%
<b>9. Treatment with PDT when the CNV is unresponsive to treatment (N=50)</b>	
a. Often add PDT	4%
b. Rarely add PDT	48%
c. Did not add PDT during the past year	46%
d. Other	2%
<b>10. Intervals between anti-VEGF treatments (N=48)</b>	
a. Every 4 weeks	56%
b. Every 6 weeks	10%
c. Bevacizumab with longer intervals than ranibizumab	21%
d. Other	13%
<b>11. Treatment of bilateral CNV (N=48)</b>	
a. Treat both eyes on the same day	13%
b. Wait 3 days between treatments	17%
c. Wait 1 week between treatments	68%
d. Other	5%
<b>12. Treatment of extensive SMH, with VA=6\60 (N=47)</b>	
a. Bevacizumab	42%
b. Ranibizumab	6%
c. Vitrectomy surgery without anti-VEGF treatment	4%
d. Pneumatic displacement (in-office)	20%
e. Other	28%
<b>13. Treatment of choice for peri-papillary CNV (N=47)</b>	
a. Laser treatment	26%
b. PDT	4%
c. Bevacizumab	44%
d. Ranibizumab	9%
e. Other	17%
<b>14. Recurrent treatment with bevacizumab one month after a stroke or a myocardial infarction (N=48)</b>	
a. Switch to PDT because of a possible increased risk for thromboembolic event	13%
b. Treat with bevacizumab	8%
c. Treat with bevacizumab, but inform patient about possible risk for thromboembolic event	63%
d. Switch to ranibizumab	8%
e. Other	8%
<b>15. Treatment with IVT injections of a patient under warfarin treatment (N=48)</b>	
a. Administer IVT injection without any special permits	83%
b. Ask permission to treat from GP and/or INR results	11%
c. Recommend withdrawal of warfarin before treatment	21%
d. Avoid treatment or recommend other treatment	2%
e. Other	0%

OR = operating room; VEGF = vascular endothelial growth factor; Bevacizumab = Avastin; CNV = choroidal neovascularization (secondary to age-related macular degeneration); GP = general practitioner; INR = international normalized ratio; IVT = intravitreal; Ranibizumab – Lucentis; OCT = optical coherent tomography; PDT = photodynamic treatment; PED = pigment epithelium detachment; SMH = submacular hemorrhage; SRF = subretinal fluid; VA = visual acuity; VEGF = vascular endothelial growth factor

## DISCUSSION

This study reflects the routine practices of Israeli retinal specialists in the diagnosis, treatment and follow-up of patients who take the anti-VEGF drugs bevacizumab and ranibizumab for various retinal diseases.

### DIAGNOSIS, TREATMENT AND FOLLOW-UP OF PATIENTS WITH AMD

For neovascular AMD, most of the specialists (56%) used both anti-VEGF drugs, but their choice was heavily (70%) influenced by the socioeconomic status of the patient. Ranibizumab is more expensive than bevacizumab and is currently not fully covered by the Israeli health funds. This choice of treatment may therefore place a substantial financial burden on patients who often require repeated injections that would cost thousands of dollars yearly. We speculate that this factor probably influences many Israeli retinal specialists (40%) to offer only bevacizumab to their patients. In the American Preferences And Trends survey, when asked about the management of classic subfoveal CNV with a VA 6/30, even more specialists (53%) voted for bevacizumab compared to 32% who chose ranibizumab as first-line treatment. In our survey, many responders apparently did not know which of the two drugs has greater efficacy (42%), or they believed that both drugs have similar efficacy (44%). The results of the CATT study (Comparison of AMD Treatments Trials), funded by the American National Eye Institute, is currently underway and will hopefully shed more light on the relative efficacy of each drug.

The time interval between treatments and the controversy over the proper timing for withholding treatment had been evaluated in a few large prospective studies. The MARINA and ANCHOR trials [4,5] included repeated monthly injections of ranibizumab all year round, regardless of whether or not there had been any clinical improvement. This treatment regimen probably results in the best visual acuity results, however performing monthly injections is not always feasible and therefore other treatment regimens were suggested. The PrONTO study [6], a smaller prospective study, investigated the efficacy of three consecutive monthly injections of ranibizumab followed by a PRN approach, guided by the results of OCT imaging. After 12 and 24 months, the outcomes of the PrONTO study were comparable to those of the MARINA and ANCHOR but with the mean frequency of dosing reduced by more than one-half, i.e., to about five injections per year.

We found that anti-VEGF drugs are only rarely given monthly all year round by Israeli retinal specialists, as suggested by the MARINA and ANCHOR studies, and that most of them use the OCT findings and their clinical examination as guides for therapeutic management of the pathology. Treatment in Israel most often starts with three consecutive monthly injections (58%), and they are administered as long as subretinal fluids or intraretinal fluids persist, regardless of

the presence of a pigment epithelial detachment (57%). The PAT survey noted similar figures, with 64% of the specialists responding that they would allow the PED to persist.

A switch from bevacizumab to ranibizumab or vice versa was recommended to the patient by most of the Israeli physicians (68–69%) after three monthly injections of one of them failing to yield improvement in the fluid status as seen on OCT. This is in contrast to the PAT survey, where only 33% of the practitioners switched to another anti-VEGF agent and 28% continued with the same agent following 8 monthly anti-VEGF injections for a CNV with a VA of 6/15.

Until recently, the main treatment options for an extensive submacular hemorrhage secondary to AMD included vitrectomy surgery or in-office pneumatic displacement of the hemorrhage [7]. Some authors suggested that injection of tissue plasminogen activator to the clot may improve the visual outcomes of vitrectomy [8]. The efficacy of anti-VEGF drugs in these cases has not yet been evaluated by randomized prospective studies, but many retinal specialists still use these drugs for this indication, sometimes in conjunction with surgery, because of the likelihood of stabilization or even improvement of VA. Almost one-half (48%) of the physicians preferred bevacizumab or ranibizumab for an extensive submacular hemorrhage with a VA of 6/60, similar to the 49% who would use the same treatment according to the American PAT survey.

For a peripapillary CNV, the only current evidence-based treatment is that of thermal laser [9], although more than one-half of retinal specialists (53%) would use bevacizumab or ranibizumab for this indication. We believe that thermal laser treatment may be appropriate for a small nasal peripapillary CNV that appears close to the optic disc, and that an anti-VEGF drug could be considered a reasonable treatment option for larger nasal-to-fovea CNVs that may threaten the macula.

Fluorescein angiography was widely used (67%) by our responders as the first diagnostic imaging modality for the detection of CNV, and it was often repeated when there were discrepancies between OCT imaging and the clinical examination of the patient.

Some trends that appeared in this survey, conducted during late 2008 to early 2009, have recently changed. For example, performing bilateral simultaneous intravitreal injections seems now much more widely acceptable [10], as well as performing three consecutive anti-VEGF injections without performing OCT and without examining the patient one month after each injection.

### MEASURES FOR ENSURING STERILITY DURING INTRAVITREAL ANTI-VEGF INJECTIONS

Endophthalmitis is very rare and is one of the most serious sight-threatening complications of intravitreal drug injections. The rate of endophthalmitis associated with anti-VEGF

PAT = Preferences and Trends

PED = pigment epithelial detachment

injection is around 0.05% per injection [5]. The results of our survey demonstrated wide variability among retinal specialists regarding the intravitreal injection technique: while some use a sterile operating room for the procedure (45%), only 67% either wash their hands or disinfect them with chlorhexidine (14%). Most physicians wear sterile gloves (90%), spread the eyelids with a speculum (100%), and administer povidone iodine before treatment (98%) and topical quinolones after (92%). Interestingly, the PAT survey revealed that 63% of American physicians did not even use sterile gloves for an in-office intraocular injection, but that 86% did instill antibiotic drops after the anti-VEGF injection. A national survey conducted in the United Kingdom and published in 2007 investigated the techniques of intravitreal injection of triamcinolone [11]. They also found a wide variability among the specialists, with 19% of retinal ophthalmologists injecting the drugs in an operating room, and 94% preparing the eye with povidone iodine [12].

Based on our own experience we recommend careful attention to aseptic techniques with meticulous preparation, the avoidance of needle contact with eyelids (by the use of a speculum and drapes), administration of povidone iodine (either on the ocular surface or in the cul-de-sac) and administration of topical antibiotics just after the injection. Recently we stopped prescribing antibiotics for 5 days after treatment, according to the results of the two prospective randomized clinical trials performed by the Diabetic Retinopathy Clinical Research Network [13], suggesting that a low rate of endophthalmitis may be achieved without the use of topical antibiotics.

#### ANTI-VEGF TREATMENT FOR DIABETIC RETINOPATHY

In this survey up to 41% of practitioners in daily clinical practice in Israel use an anti-VEGF drug after 1–2 conventional laser treatments have failed. This survey was, however, conducted before the recently published results of the Diabetic Retinopathy Clinical Research Network study [14]. That large randomized controlled trial found that the difference in mean change in VA from sham plus laser treatment at 2 years was +5 letters for the ranibizumab plus-prompt (within 1 week) laser group ( $P = 0.01$ ), +7.2 letters for the ranibizumab plus-deferred ( $\geq 24$  week) laser group ( $P < 0.001$ ), and -1.6 for the triamcinolone acetate plus-prompt laser group ( $P = 0.43$ ). As a result, treatment with ranibizumab recently became the standard of care for patients with CSME. Although previous reports had suggested that intravitreal triamcinolone acetate may play an important role in the treatment of CSME, the DRCRnet study found that ranibizumab yielded better VA results (or comparable results in a pseudophakic patients subgroup analysis) and that triamcinolone had more side effects, such as elevated intraocular pressure and cataract progression [14]. Our survey

likewise demonstrates the trend of preferring combined laser and anti-VEGF treatment over triamcinolone in CSME.

For patients with PDR, currently the only evidence-based treatment of HRC PDR is laser treatment [15]: over one-half (54%) of our responders combined it with an anti-VEGF drug for patients who demonstrate persistent retinal neovascularization despite laser treatment. Some authors would even consider this treatment before administering PRP [16].

#### ANTI-VEGF TREATMENT FOR VASCULAR OCCLUSIONS, NEOVASCULAR GLAUCOMA AND MYOPIC CNV

Most of the specialists who participated in our survey reported that they would treat a non-ischemic CRVO with a VA of 6/15 only after the appearance of macular edema (60%). Monthly follow-up with OCT and PRN injections is the mainstay of treatment in Israel according to our survey (94%). In a perfused BRVO, when the VA is preserved (6/8.5) and macular edema exists after 3 months, most physicians would allow only follow-up or perform laser grid treatment (64%). However, when the VA is relatively poor (6/15), most of them (58%) would administer anti-VEGF treatment or combine it with focal laser treatment. The popularity of anti-VEGF drugs is also increasing for the treatment of neovascular glaucoma (88%) and myopic CNV (73%), but not for non-arteritic anterior ischemic optic neuropathy (2%).

Until recently, there was no effective treatment for CRVO [17]. The Central Retinal Vein Occlusion study (CRVOS), that was published in 1995 [18], had been the only available large prospective randomized controlled trial and its results were not impressive. That study recommended laser treatment with PRP for neovascularization of the iris or the angle. Macular grid laser treatment was not found to be beneficial for treating macular edema, although a positive trend was demonstrated in patients under the age of 65. The later results of the CRUISE study that compared ranibizumab and sham injections for macular edema secondary to CRVO showed that after 6 months of repeated monthly injections of ranibizumab (0.3 mg, 0.5 mg), 45–47% of treated patients gained 3 or more visual acuity lines compared to only 17% in the sham group ( $P < 0.0001$ ) [19]. The results of the CRUISE study were published after our survey was launched. This study suggests that monthly injections of an anti-VEGF drug may be beneficial in patients with macular edema secondary to CRVO, regardless of their VA, and probably given the sooner the better, as opposed to the PRN method currently accepted in Israel (at least for the first 6 months after diagnosis). As for BRVO, the results of BVOS (the Branch Retinal Vein Occlusion Study), published in the mid 1980s, suggested that treatment of macular edema should be delayed for at least 3 months to permit maximal spontaneous resolution of the edema and of the intraretinal blood. Photocoagulation for macular edema was found to be beneficial for eyes with vision falling in the 6/12–6/60 range if the perifoveal retinal

DRCRnet = Diabetic Retinopathy Clinical Research Network

capillaries were intact [20]. The recently published BRAVO study randomized patients with BRVO and macular edema to monthly intravitreal injections of ranibizumab (0.3 mg, 0.5 mg) and sham. After 6 months, the treatment groups had gained 16.6 letters (0.3 mg) and 18.3 letters (0.5 mg) compared to the sham group that gained only 7.3 letters ( $P < 0.0001$ ), although the control group did not receive focal laser treatment [21]. The findings of the BRAVO study may also imply that more aggressive treatment for macular edema secondary to BRVO should be considered, even in early stages (e.g., monthly injections as opposed to PRN, without watchful waiting for the macular edema to resolve), in order to avoid recurrence of the macular edema as well as to maintain optimal VA.

## CONCLUSIONS

According to our experience and in the light of this survey, we propose the following general recommendations: start treating a new choroidal neovascularization secondary to age-related macular degeneration with three consecutive anti-vascular endothelial growth factor injections, followed by monthly PRN treatments. Treat until the intraretinal edema and subretinal fluids resolve, but allow a pigment epithelial detachment to persist. Consider switching between anti-VEGF drugs when there is deterioration in the visual acuity or subretinal/intraretinal fluid status, despite recurrent injections of one of the anti-VEGF drugs. Regarding the injection technique, perform the procedure in an outpatient clinic, using a lid speculum and a sterile nylon wrap. Povidone-iodine should be administered before treatment and topical antibiotics at the end of the procedure. For CSME, start with anti VEGF therapy and if needed combine focal laser treatment according to the DRCRnet recommendations [14]. For CRVO/BRVO with macular edema be liberal with repeated injections of anti-VEGF drugs, and for BRVO add focal laser treatments if required.

Our survey revealed many similarities between the routine practices of retinal specialists in Israel and in the United States, but many questions remained unanswered. A few large prospective randomized controlled trials are currently underway with the aim of providing evidence-based answers to some of the controversies covered in our survey. Until their results are made available, however, ophthalmologists must depend upon their own personal experience and the current knowledge of the ophthalmic use of anti-VEGF drugs and surveys such as ours when choosing among the various treatment strategies.

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