

Clinical Practice Guideline

Intravitreal Injection of Anti-vascular Endothelial Growth Factor Agents for Ocular Vascular Diseases: Clinical Practice Guideline

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Received: 19-08-2017

Accepted: 17-12-2017

J Ophthalmic Vis Res 2018; 13 (2): 158–169

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How to cite this article: Nikkhah H, Karimi S, Ahmadi H, Azarmina M, Abrishami M, Ahoor H, *et al.* Intravitreal injection of anti-vascular endothelial growth factor agents for ocular vascular diseases: Clinical practice guideline. *J Ophthalmic Vis Res* 2018;13:158-69.

Access this article online

Quick Response Code:



Website:
www.jovr.org

DOI:
10.4103/jovr.jovr_50_18

Abstract

Purpose: To provide the clinical recommendations for the administration of intravitreal anti-vascular endothelial growth factor (VEGF) drugs especially bevacizumab for ocular vascular diseases including diabetic macular edema, neovascular age-related macular degeneration, myopic choroidal neovascularization, retinal vein occlusion and central serous chorioretinopathy.

Methods: Twenty clinical questions were developed by the guideline technical committee. Relevant websites and databases were searched to find out the pertinent clinical practice guidelines to answer the questions. The technical committee provided possible answers (scenarios) according to the available evidences for each question. All scenarios along with their levels of evidence and the supported articles were sent to the experts for external review. If the experts did not agree on any of the scenarios for one particular clinical question, the technical committee reviewed all scenarios and their pertinent evidences and made the necessary decision. After that, the experts were asked to score them again. All confirmed scenarios were gathered as the final recommendations.

Results: All the experts agreed on at least one of the scenarios. The technical committee extracted the agreed scenario for each clinical question as the final recommendation. Finally, 56 recommendations were developed for the procedure of intravitreal anti-VEGF injection and their applications in the management of ocular vascular diseases.

Conclusion: The implementation of this guideline can standardize the management of the common ocular vascular diseases by intravitreal injection of anti-VEGF agents. It can lead to better policy-making and evidence-based clinical decision by ophthalmologists and optimal evidence based eye care for patients.

Keywords: Age-related Macular Degeneration; Anti-vascular Endothelial Growth Factor; Intravitreal Injection; Diabetic Macular Edema; Retinal Vein Occlusion

INTRODUCTION

Ocular vascular diseases are among the leading causes of visual impairment (VI) and blindness worldwide.^[1] Diabetic retinopathy (DR), diabetic macular edema (DME), age-related macular degeneration (AMD), and retinal vein occlusion (RVO) are the most prevalent ocular vascular disorders. DR is an important cause of acquired vision loss among the world's working-age population.^[2-4] It is estimated that the number of people with DR and sight-threatening DR will increase to 191 million and 56.3 million, respectively by 2030.^[5] In Iran, a population-based study in Yazd province reported that DR accounted for 50% of blindness and 17% of VI.^[6] AMD is also the main cause of severe VI among the elderly globally.^[7,8] Due to the worldwide aging of the population, the global burden of AMD is expected to increase, affecting an estimated 196 million people in 2020 and 288 million in 2040.^[9]

In recent years, the introduction of vascular endothelial growth factor (VEGF) inhibitors (also known as anti-VEGFs) has revolutionized the treatment of—and prognosis for—individuals with AMD, DME, and RVO.^[10-20] Anti-VEGFs have an important role in treating common vision-threatening retinal diseases and multiple studies have demonstrated the efficacy of intravitreal anti-VEGF injection for management of these diseases.^[21-23] Thirty percent of patients with neovascular AMD reported an increase in visual acuity, and 90% reported preserved visual acuity following intravitreal anti-VEGF injections.^[13,24-26] The off-label anti-VEGF

drug (bevacizumab; Avastin®, Genentech/Roche), and US "Food and Drug Administration" approved anti-VEGF agents including ranibizumab (Lucentis®; Genentech/Novartis), and aflibercept (Eylea; Regeneron/Bayer)—are used in Iran; however, the most common one is bevacizumab due to the lower cost and the insurance coverage. Although the safety and efficacy of these agents have been already reported, their rare complications can be devastating, leading to permanent visual loss.^[21-23,27,28] On the other hand, anti-VEGF injections need to be repeated due to their short-term efficacy.^[29]

National clinical practice guidelines (CPGs) are developed to optimize the efficacy of interventions and to provide equity in access to treatment for all inhabitants of a country. CPGs contain clinical recommendations developed on the basis of high-level available evidence that are adapted considering their efficacy, safety and cost of interventions, and the nation's requirements. CPGs can help physicians and patients make appropriate decisions. They can also guide policymakers to improve the quality of care and reduce the costs.^[30,31]

To the best of our knowledge, previously published protocols have specifically focused on intravitreal injection techniques, and there has been no CPG focused on the indications of anti-VEGF agents for ocular vascular diseases. This CPG was developed under the supervision of the Office for Healthcare Standards, Deputy of Curative Affairs, Iran Ministry of Health and Medical Education to help choosing the appropriate anti-VEGF agent and an appropriate interval for each

individual. Furthermore, the recommendations of this CPG will be useful for increasing the safety of the injections by providing specific recommendations. The recommendations in this CPG were also revised based on the customized criteria to help ophthalmologists make the best evidence-based clinical decisions specifically applicable to Iran.

METHODS

This CPG for intravitreal injection of anti-VEGF agents for the treatment of ocular vascular diseases was developed at the Knowledge Management Unit (KMU) at the Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The technical committee comprised the steering technical committee, eight retina specialists, three ophthalmologists, four Master of Science degree holders in optometry; and the head of the Office for Healthcare Standards and Deputy of Curative Affairs, Iran Ministry of Health and Medical Education.

Finding the Relevant Clinical Practice Guidelines

A large number of websites and databases such as Guidelines International Network, National Institute for Clinical Excellence, National Guidelines Clearinghouse, Scottish Intercollegiate Guidelines Network, New Zealand Guidelines Group, National Health and Medical Research Council, Cochrane, Bandolier, Canadian Agency for Drugs and Technologies in Health, Trip Database, PubMed, Google Scholar, SID, Medlib, and Magiran were searched to find the pertinent CPGs.

Screening the Extracted Clinical Practice Guidelines

Two protocols and CPGs, including “Guidelines for intravitreal injections procedure” (The Royal College of Ophthalmologists 2009) and “Intravitreal injection” (American Academy of Ophthalmology 2015) were extracted.^[32,33] The researchers chose the reference

guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE) tool.^[34] These guidelines focused more on the intravitreal injection procedure.

Designing the Clinical Questions

Twenty clinical questions were designed by the technical committee. Two reference guidelines were reviewed to find the answers to the questions. The questions, along with the answers were extracted from the reference guidelines and were entered into Table 1.

Appraising and Summarizing Additional Evidence

Relevant articles were excerpted from the above-mentioned databases to provide additional evidence to answer the clinical questions. These focused on indications of anti-VEGF agents for treating ocular vascular diseases. The details of this evidence were summarized and entered into Table 2. The level of evidence was determined based on the parameters described in Table 3.

Providing Scenarios

The technical committee developed all scientifically possible answers (scenarios) based on the available evidence for each question and entered them into Tables 4 and 5.

External Review (Consensus)

All scenarios—along with Tables 1, 2, 4, and 5, and references—were sent to the retina specialists who were experts in this field. We requested them to review each question’s different scenarios and specify the best one by score. The score of 1 represented the worst and the score of 9 represented the best choice, considering the clinical benefits and customizing criteria.

Analyzing the Scores and Providing Final Recommendations

The level of agreement for each scenario was determined

Table 1. Analysis of recommendations

Question (E)	P	I	C	O	Type of question	Referenced guidelines	Phrase of recommendation	Level of evidence	Inconsistency of recommendations	Technical breakthrough	New systematic review	New studies
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This is the blank table template. P, patient or population; I, intervention; E, exposure; C, comparison; O, primary outcomes

Table 2. Analysis of evidences

Evidence code	P	I (E)	C	O	Effect size	Statistical values	Level of evidence
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This is the blank table template. P, patient or population; I, intervention; E, exposure; C, comparison; O, primary outcomes

according to the experts' scores. The agreed-upon scenario for each clinical question was considered as the final answer. If the experts did not agree on any of the scenarios of one clinical question, the technical committee made the necessary corrections by reviewing the evidences again. After that, we asked experts to score them again.

All confirmed scenarios were gathered as the final recommendations that were provided in the results along with their evidence levels (ELs).

RESULTS

General Recommendations and Recommendations for Intravitreal Anti-VEGF Injection Procedure

1. Anti-VEGFs should be used cautiously in patients with a history of systemic vascular diseases such as stroke or myocardial infarction (MI) during the past three months. Appropriate consultations should be made before administration of anti-VEGF injections.^[35-40]

- EL: Consensus
- 2. Bilateral intravitreal injection is not recommended. However, it is not contraindicated and can be performed at the surgeon's discretion. Separate gloves, surgical preps, and vials with different batches should be used for each eye.^[41]
EL: Consensus
- 3. The procedure can be conducted in the outpatient sterile operating room.
EL: Consensus
- 4. Individual sterile gloves should be used for each patient.^[41]
EL: Consensus
- 5. Physicians should wear surgical masks when performing the injection. Physicians and patients should minimize speaking during the procedure.^[41-42]
- 6. The patient's name, anti-VEGF agent type, and laterality should be checked immediately before intravitreal injection.^[41]
- 7. It is recommended that topical anesthetics be used before prep and drapes to minimize patient discomfort.^[33,41]
- 8. Eyelids and the lid margins should be sterilized with povidone-iodine (10%).^[41]
- 9. The eyelids should be retracted from the intended injection site by a sterile speculum and the needle should not have any touch with the lid margins.^[41]
EL: Consensus
- 10. Diluted povidone-iodine (5%) should be applied to the conjunctival injection site for at least 30 seconds before injection.^[41]
- 11. It is recommended that a 29 or 30 -gauge needle be used to perform anti-VEGF intravitreal injections.^[41]
EL: Consensus
- 12. It is recommended that intravitreal injection be performed between the horizontal and vertical rectus muscles at the pars plana 3 and 4mm posterior to the limbus in pseudophakic and aphakic eyes, prospectively. However, the quadrant selection can be chosen using

Level of evidence	Type of evidence
I	Meta-analysis Systematic reviews Randomized clinical trial
II	Clinical trial Well-designed cohort Well-designed case control Cross-sectional
III	Surveys Descriptive Case series
IV	Expert opinion, consensus

Question	Phrase of recommendation	Level of evidence	Costs	Clinical effectiveness of the recommendation			Clinical benefit score		
				Side effects	Benefits	Effect size	Low	Moderate	High

This is the blank table template. P, patient or population; I, intervention; E, exposure; C, comparison; O, primary outcomes; Low: Score 1-3; Moderate: Score 4-6; High: Score 7-10

Question	P I C O	Type of the question	Phrase of recommendation	Adaptability of the recommendation			Adaptation score		Total score
				Applicability	Acceptability	Compatibility/ External validity	Low	Moderate	

This is the blank table template. P, patient or population; I, intervention; E, exposure; C, comparison; O, primary outcomes; Low: Score 1-3; Moderate: Score 4-6; High: Score 7-10

patient-specific considerations and preference of the physician. In the majority of settings, a simple perpendicular injection approach is preferred.^[41]

EL: Consensus

13. It is not necessary to prescribe topical antibiotics immediately and/or for a few days after intravitreal injection. A growing body of evidence discourages the post-injection antibiotics.^[43-48]

EL: Consensus

14. It is recommended that intravitreal bevacizumab, aflibercept and ranibizumab be injected at a dosage of 1.25 mg/0.05 ml, 2 mg/0.05 ml and 0.5 mg/0.05 ml, respectively in patients with ocular vascular diseases.^[20,49]

15. An information brochure about the signs and symptoms of post-injection complications and emergency contact details should be presented to patients after injection. Patients should be aware of the necessity of urgent visit in case of ocular pain and visual impairment. Therefore, a routine first day post-injection visit is not necessary.

EL: Consensus

16. In patients at risk for optic nerve damage due to the rise in intraocular pressure (IOP) after intravitreal injection, topical anti-glaucoma drugs or anterior chamber paracentesis should be administered.^[50]

EL: Consensus

17. One of the following strategies can be used for injecting intravitreal anti-VEGF agents based on the clinician's priority:^[51-58]

a. Three consecutive monthly injections, followed by as-needed injections (PRN)

b. Three consecutive monthly injections, followed by treatment intervals that will be sequentially lengthened by 2 weeks. However, the interval should not exceed 3 months (treat and extend)

c. One injection at first followed by PRN injections

EL: Consensus

18. Although the rhegmatogenous retinal detachment (RRD) following intravitreal anti-VEGF injections is rare (incidence = 0.013%), the risk of RRD should be considered, especially among myopic patients, who should be monitored after each injection.^[45,59-61]

EL: II

Recommendations for Management of Retinal Vascular Diseases

Diabetic macular edema

General recommendations

1. All anti-VEGF agents, including intravitreal ranibizumab (IVR), intravitreal bevacizumab (IVB), and intravitreal aflibercept are effective in inducing visual improvement and central macular

thickness (CMT) reduction.^[21,62,63]

EL: I

2. Evidence showed that the 2-year visual outcomes of IVB, IVR and aflibercept are the same in patients with baseline visual acuity of 20/40 or better. Among patients with baseline visual acuity of 20/50 or worse, intravitreal injection of aflibercept resulted in the best visual outcomes compared with bevacizumab and ranibizumab at 1-year follow-up. However, the superiority of aflibercept disappeared at year 2.^[21]

EL: I

3. According to the literature, short- and long-term safety and efficacy of the IVB injection has been proved in DME patients.^[64]

EL: I

4. Intravitreal injection of bevacizumab is recommended as the first line treatment in patients with diabetes due to its effectiveness in reducing the VEGF level in the ocular media.^[65-67]

EL: I

Indications

5. Periodic injection of IVB is recommended for patients with naive DME.^[67-81]

EL: I

6. In patients with chronic DME, 5-6 monthly injections of IVB are recommended.^[82]

EL: Consensus

7. IVB injection is recommended in patients with diffuse DME.^[71,80,83, 84,85]

EL: II

8. Three loading doses of IVB is recommended in patients with refractory DME.^[86,87]

EL: I

9. Patients with proliferative diabetic retinopathy (PDR) who have been scheduled for vitrectomy may receive intravitreal anti-VEGF injection within one week before surgery to reduce intraoperative and early postoperative hemorrhage.^[88]

EL: I

10. Intravitreal injection of anti-VEGF drugs may increase the risk of tractional retinal detachment in patients with extensive fibrovascular tissue. Therefore, it is recommended to perform the intravitreal injection 3-5 days before surgery in this subset of patients.^[89-96]

EL: Consensus

11. Either panretinal photocoagulation (PRP) or the combination of IVB and PRP is recommended in patients with high risk PDR.^[97-101]

EL: I

Comorbidities

12. DME should have been treated before cataract surgery. In addition, IVB may be injected intraoperatively.^[102-104]

EL: I

Neovascular age-related macular degeneration

General recommendations

1. Considering the effectiveness, safety, and rare and transient complications of IVB and other anti-VEGF drugs injections, it is recommended these drugs be used to treat patients with neovascular AMD.^[62,105]
EL: I
2. It is recommended that patients be given sufficient information regarding the need for repeated, frequent intravitreal anti-VEGF injections for the treatment of neovascular AMD.^[106]
EL: III
3. Multiple intravitreal anti-VEGF injections do not reduce retinal nerve fiber layer thickness. Therefore, it is recommended that intravitreal anti-VEGF injections be repeated as needed.^[107]
EL: III
4. In unilateral anti-VEGF injections, it is recommended that physicians consider the condition of the fellow eye.^[108,109]
EL: I
5. It is also recommended that IVB injection be used to treat patients with active neovascular AMD coexisting with retinal pigment epithelium (RPE) tear to improve their visual acuity.^[110]
EL: III

Risk factors

6. It is recommended that risk factors for poor visual acuity outcome—such as older age, larger choroidal neovascularization (CNV), and elevated pigment epithelial detachment (PED)—be considered before treating patients with neovascular AMD and inform them about the possibility of less favorable visual outcomes.^[45,59-61]
EL: II

Complications

7. In patients with neovascular AMD who are undergoing anti-VEGF treatment, there is a risk of scar formation especially in the cases of classic CNV, increased central retinal thickness, and the presence of excessive subfoveal fluids or deposits.^[111]
EL: II
8. To stabilize the visual and anatomic (CMT) outcomes in patients with persistent neovascular AMD (unresponsive to IVB), it is recommended that IVR or aflibercept injections be used. The presence of intraretinal fluid has an adverse effect on visual acuity improvement. However, residual subretinal fluid does not impede visual improvement and may even improve the visual acuity prognosis.^[58,111,112]
EL: I

Polypoidal choroidal vasculopathy

1. Combined photodynamic therapy and intravitreal anti-VEGF injection is recommended for treatment of patient with polypoidal choroidal vasculopathy.^[113,114]
EL: I

Myopic choroidal neovascularization

General recommendations

1. It is recommended that intravitreal anti-VEGF drugs be used in patients with myopic CNV to improve the vision and to reduce CMT.^[115,116]
EL: I
2. In patients with myopic CNV, it is recommended that IVB be injected first, and photodynamic therapy (PDT) should then be performed in cases resistant to the treatment.^[115-117]
EL: I

Risk factors

3. Vision improvement following anti-VEGF intravitreal injections was higher in patients with myopic CNV who were aged less than 50 years. Therefore, it is recommended that funduscopy be performed in young patients with high degrees of myopia to ensure early detection and timely treatment of CNV.^[118]
EL: III
4. Older patients with high degrees of myopia and subfoveal CNV, and/or those with higher levels of myopia, and/or those with primary extensive CNV, hemorrhage, and choroidal thickness reduction are at risk of CNV recurrence after IVB treatment. Therefore, it is recommended that they undergo periodic examinations at appropriate intervals.^[119,120]
EL: III

Other types of choroidal neovascularization

5. Due to the effectiveness and safety of intravitreal anti-VEGF injection in pediatric patients with CNV, it is recommended that these drugs be used for pediatric's CNV.^[121]
EL: III
6. It is recommended that IVB injections be used for patients with idiopathic subfoveal CNV or cases with previous inflammation.^[115,116,122-124]
EL: I

Branch retinal vein occlusion

General recommendations

1. IVB is more effective in terms of visual acuity improvement and CMT reduction compared with the other treatment modalities (IVT, laser) for treating branch retinal vein occlusion (BRVO). Therefore, IVB injection is recommended for patients with macular edema secondary to BRVO.^[125-130]
EL: I

2. Since IVB or IVR injection has long-term effects on visual acuity improvement in patients with perfused BRVO, it is recommended that these agents be injected in patients with macular edema secondary to perfused BRVO.^[131]
EL: I
3. Better therapeutic effects can be achieved in patients with macular edema due to BRVO after early treatment (within two weeks after the diagnosis). Therefore, it is recommended that IVB be injected in these patients early after diagnosis.^[132]
EL: III

Procedure

4. In patients with macular edema due to BRVO, four IVB injections within 6 months are recommended.^[133-138]
EL: I

Risk factors

5. Lower baseline visual acuity, older age, longer duration, and non-perfused BRVO are risk factors for visual improvement after IVB injection. Hence, it is recommended that these risk factors be considered and that patients be informed before injections.^[139]
EL: III
6. IVB in BRVO patients with vitreomacular adhesion (VMA) leads to better visual and anatomical outcomes (more CMT reduction). Therefore, VMA is not considered as a risk factor in this regard.^[140]
EL: III

Central retinal vein occlusion

General recommendations

1. Anti-VEGF intravitreal injection is an effective and safe treatment for macular edema secondary to central retinal vein occlusion (CRVO) for up to 2 years; delayed treatment would lead to poor visual outcome.^[132]
EL: III
2. Despite acceptable short-term visual outcomes after intravitreal steroid injection and intraocular steroid implants in patients with CRVO, possible side effects include cataract formation and increased IOP. Therefore, anti-VEGF agents are the preferred treatment in these cases.^[141-148]
EL: I

Procedure

3. In patients with macular edema secondary to CRVO, eight IVB injections within 12 months are recommended.^[133-138]
EL: I

Risk factors

4. In patients with CRVO who have disruption of the external limiting membrane (ELM), IVB or IVR

injection is associated with reduced visual acuity improvement. Therefore, it is recommended that the integrity of the ELM be evaluated before treatment to determine the prognosis for visual outcomes.^[149]
EL: III

Central serous chorioretinopathy

1. The use of anti-VEGF intravitreal injections for treating eyes with central serous chorioretinopathy (CSC) remains controversial. Therefore, recommendations regarding intravitreal anti-VEGF injections for the treatment of CSC are summarized as follows:^[150-154]
 - It is recommended that patients with acute CSC only be followed up
 - In patients with chronic CSC, half-dose photodynamic therapy is recommended
- EL: I

DISCUSSION

Anti-VEGF agents have changed the treatment pattern for ocular vascular diseases.^[1] The importance of timely treatment of the diseases previously described through the use of VEGF inhibitors for preventing vision loss^[3] and the lack of CPGs for defining proper indication of these agents encouraged us to develop such CPG.^[3] Development of CPGs for intravitreal injection of anti-VEGF agents in ocular vascular diseases was undertaken at KMU, Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, in collaboration with the Ministry of Health and Medical Education.

This guideline includes 56 recommendations for the indication and management of DME, neovascular AMD, myopic CNV, RVO, and CSC using anti-VEGF agents.

Providing multiple scenarios for each clinical question was the strength of our research. In this approach, we presented different treatment modalities based on available evidence and asked experts to choose the best treatment strategy considering clinical and individual criteria. Therefore, we could evaluate their agreement on answers to each clinical question more accurately.

Experts agreed on at least one of the scenarios for each clinical question. Thirteen questions had more than one agreed-upon scenarios. These questions, along with their scenarios, were reviewed again by the technical committee to select the best scenario as the final recommendation.

The role of anti-VEGF agents in treatment of CSC has remained controversial and there is limited high-level evidence for managing this condition. Although a number of scenarios were developed in this regard, most of them were refused by experts in the external review process. Future multicenter research is needed

to determine the effect of anti-VEGF agents in patients with CSC.

In conclusion, the CPG for intravitreal injection of anti-VEGFs for ocular vascular diseases was developed using existing high-level evidence to improve the equity in access to the best available evidence-based treatments for all society members. At the national level, this work complies with the strategic objective of the Ministry of Health and Medical Education. This objective includes developing, adapting, and implementing the CPGs and extending healthcare services.

Financial Support and Sponsorship

Nil.

Conflicts of Interest

There are no conflicts of interest.

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