Viewpoint: Use of bilateral anti-VEGF injections
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VEGF, vascular endothelial growth factor.
Objectives

- To provide an overview of bilateral anti-VEGF treatment
- To identify areas requiring guidance
- To present the recommendations of the Vision Academy on this topic

The Vision Academy provides ophthalmic specialists with a forum to share existing skills and knowledge, build best practice, and lead the wider community in the drive towards optimized, compassionate patient care.

Through their collective expertise, the Vision Academy seeks to provide guidance for best clinical practice in the management of retinal disease, particularly in areas with insufficient conclusive evidence.

**QUESTION**

What are the challenges for bilateral anti-VEGF treatment?
Background
The impact of nAMD

nAMD is the leading cause of blindness in developed countries (~2/3 of new cases in the elderly)¹

Bilateral nAMD significantly reduces patients’ quality of life²,³
- QoL scores comparable to or worse than several other chronic and/or debilitating diseases, such as colorectal cancer and multiple sclerosis²
- Significantly worse overall well-being and more anxiety and depression symptoms reported³

Bilateral nAMD is associated with a considerable societal cost burden, with an increased need of daily living assistance for patients with nAMD³

AMD, age-related macular degeneration; nAMD, neovascular AMD; QoL, quality of life; VA, visual acuity; VEGF, vascular endothelial growth factor.
1 in 4 unilateral AMD cases progress to bilateral disease within 5 years

- Joachim et al. (2017): Pooled data analyses of three prospective population-based cohorts, the Blue Mountains Eye Study, Beaver Dam Eye Study, and Rotterdam Study
- Progression to bilateral disease was assessed in participants with early or late unilateral AMD
- AMD factors associated with disease progression were assessed using logistic regression models while simultaneously adjusting for other significant risk factors
- AMD risk factors, including smoking, were significantly associated with progression to bilateral disease

AMD, age-related macular degeneration.
Bilateral disease is associated with reduced QoL

- Soubrane et al. (2007): A cross-sectional study of 401 patients with bilateral nAMD and 471 individuals without nAMD was conducted in five countries.

- Individuals completed a telephone survey, including:
  - National Eye Institute 25-Item Visual Function Questionnaire
  - EuroQol instrument
  - Hospital Anxiety and Depression Scale
  - History of falls and fractures
  - Healthcare resource utilization

Compared to individuals without nAMD, patients with bilateral nAMD reported:

- 45% worse vision-related functioning
- 13% worse overall well-being
- 30% more anxiety
- 42% more depression symptoms

nAMD, neovascular age-related macular degeneration; QoL, quality of life.
Anti-VEGF therapy is the gold standard for nAMD

- Injection of anti-VEGF agents is the gold-standard treatment for several common retinal vascular disorders
- Anti-VEGF clinical trials have demonstrated their efficacy in maintaining and improving vision in patients with nAMD
- Clinical trials and real-life experience have demonstrated that single intravitreal injections carry a very low risk of serious complications when proper procedures and precautions are followed

- However, local complications and adverse systemic effects have been reported with anti-VEGF therapy
Bilateral anti-VEGF treatment

“Simultaneous or consecutive administration of anti-VEGF treatment, with both injections administered during the same patient visit”

CHALLENGE REQUIRING VISION ACADEMY GUIDANCE

Is it possible and reasonable to conduct bilateral injections?
Only a minority of patients currently receive bilateral injections on the same day

- Giocanti-Auregan *et al.* (2016): In patients with nAMD, bilateral injections were administered:
  - The same day as first administration in 13.8% of cases
  - Within a time interval of >1 day and <1 month after first administration in 19% of cases
  - >1 month after first administration in 67.2% of cases
Pros and cons of bilateral injections

**Pros:**
- Compared to unilateral treatment, bilateral treatment significantly decreases the patient and clinic burden.
- A patient with active bilateral disease often requires twice-monthly/multiple visits to their treating ophthalmologist for an extended period of time.
- This high frequency of unilateral treatment poses a significant burden on patients' time and productivity, and on the healthcare system.
- Treating each eye at separate visits adds significantly to the patient and clinic burden.

**Cons:**
- Potentially higher safety risks due to increased dose and the additional procedure remain a concern.
- Increases in dose due to bilateral injections may cause an increased risk of local and systemic adverse events.
- Performing the same procedure twice in 1 day may compromise aseptic procedures.
- Bilateral endophthalmitis and vision loss is a significant concern for physicians.

**Challenge Requiring Vision Academy Guidance:**
Is it possible and reasonable to conduct bilateral injections?
Bilateral anti-VEGF treatment
Bilateral intravitreal anti-VEGF therapy is well tolerated

- **Davis et al. (2010):** A consecutive series of 254 eyes in 127 patients who received bilateral same-day anti-VEGF injections of either bevacizumab or ranibizumab between January 1, 2007 and July 1, 2008.

- The incidence of adverse effects was low, with only four events reported:
  - Three patients reported pain and/or tearing following injection and one patient had an episode of supraventricular tachycardia requiring transfer to a local hospital.

- No eyes developed endophthalmitis, anterior chamber cell or flare, vitritis, vitreous hemorrhage, retinal detachment, or RPE tear.

- No patients had a myocardial infarction or stroke.

- Very few patients switched back to the staggered injection, although no formal satisfaction questionnaire was administered.

RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

Bilateral anti-VEGF was preferred and did not increase the rate of systemic adverse events

- **Mahajan et al. (2011):** In this retrospective case-control study, patients with AMD who received bilateral anti-VEGF injections on the same day over a 23-month period were compared with patients who received injections in only one eye
  - A total of 452 bilateral injections (904 injections overall) were performed in the bilateral group, with an average of 4.4 bilateral injections (8.8 injections overall)
  - In the unilateral group, 1009 unilateral injections were performed overall, with an average of 10.2 injections per patient
- There was no difference in AE rates in the bilateral and unilateral injection groups
- 91 of 100 patients receiving bilateral injections expressed a preference for same-day versus separate day injections
- Of 85 patients who previously received unilateral injections, 82 either disagreed or strongly disagreed that bilateral injections caused more discomfort

Patients who received bilateral intravitreal injections of an anti-VEGF agent had the same rate of systemic AEs as those who received unilateral injections

**CHALLENGE REQUIRING VISION ACADEMY GUIDANCE**
Is it possible and reasonable to conduct bilateral injections?
Bilateral anti-VEGF injections can be delivered safely following standard aseptic techniques

Bilateral endophthalmitis and vision loss is a significant concern for physicians.\(^1\)

- **Woo et al. (2012):** A retrospective review of the medical records of 135 patients who received 574 bilateral same-day intravitreal injections.
- Molecular bacterial screening was performed.
- The bacterial molecular surveillance system demonstrated the safety of bilateral same-day intravitreal injections when drugs were drawn from a single vial and injected using separate syringes or needles.

- **Abu-Yaghi et al. (2014):** A retrospective case series study of 74 patients receiving simultaneous bilateral intravitreal injections.
- Bilateral same-session intravitreal injections using a separate povidone-iodine preparation, speculum, needle, and syringe for each eye were well tolerated.
- No patients requested alternating unilateral injections after receiving bilateral injections.

Bilateral intravitreal injections can be delivered safely on the same day via a standard aseptic protocol.

**QUESTION**
What precautions and procedures should be observed?

VEGF, vascular endothelial growth factor.
Clinical challenges
Clinical challenges requiring guidance

Click on a section

Bilateral anti-VEGF treatment
• Is it possible and reasonable to conduct bilateral injections while observing appropriate procedures and precautions?

Separate procedures
• Should the second injection be treated as a separate procedure within the same visit?

Treatment batches
• How can the risk of adverse events in both eyes be minimized?

Patient preference
• When should patient preferences be taken into account?

VEGF, vascular endothelial growth factor.
Vision Academy recommendations
It is possible and reasonable to conduct bilateral injections

There is no evidence to date suggesting that there is an increased risk of ocular AEs with bilateral treatment compared with unilateral treatment

- There is also no evidence that bilateral injections alter the risk of systemic AEs associated with intravitreal injection of anti-VEGF agents
- To manage the risks associated with the injection procedure, it is recommended to follow the guidance outlined in the following slides, in cases where bilateral treatment is deemed appropriate

Studies have demonstrated no increased risk of ocular or systemic AEs with bilateral treatment compared with unilateral treatment1-6

General consensus

It is possible and reasonable to conduct bilateral injections while observing appropriate procedures and precautions

AE, adverse event; VEGF, vascular endothelial growth factor.
The second injection should be treated as a separate procedure within the same visit

Treating each injection as a completely new procedure can help minimize the risk of procedure-related complications or cross-contamination

- After the first injection, the patient should be prepared again, following the recommended procedure for intravitreal injections

This procedure should include:

- Surgical disinfection of the surgeon’s hands and/or application of new sterile gloves
- Application of povidone-iodine* to the conjunctival sac
- Cleaning of the periocular skin, eyelid margins, and eyelashes with povidone-iodine*
- Use of sterile equipment, including masks, eyelid speculum, forceps, and ophthalmic drape (if used)\(^1\)\(^-\)\(^3\)

These steps can help ensure each injection is a completely new procedure, which will minimize the risk of procedure-related complications or cross-contamination

Steps should be taken to ensure each second injection is a completely new procedure

\*Or a suitable alternative such as chlorhexidine.


General consensus
Products for the second injection should not be from the same batch

In compounded agents, sterility may be compromised due to the additional steps required to aliquot them into individual doses

- To minimize this risk, the products administered to each eye should be from different batches

- Commercial products are supplied in packages for single use only, and are produced in very large lot sizes, so use of different batches may not be feasible
  - Where this is the case, separate packages from the same batch may be used

General consensus

It is essential to avoid the risks of a contaminated product being administered to both eyes

Using products from different batches, where possible, is recommended to minimize risks of contamination to both eyes

Extra care is required for patients who require bilateral injections at the first visit

Receiving injections in both eyes at the first visit may be an intimidating prospect

- The patient’s preference should always be taken into account when deciding whether to treat both eyes at this time

As there is a small risk that an idiosyncratic hypersensitivity response may occur after the first treatment, additional considerations apply at the first visit:

- If possible, avoid bilateral injections until the tolerability of the agent has been ascertained

- If it is essential to administer bilateral treatment at the first visit, consider staggering the injections to allow time for acute hypersensitivity responses to manifest, by administering the first injection at the beginning of the clinic visit and the second at the end

General consensus

The preference of the patient and idiosyncratic hypersensitivity risks should always be taken into account

Summary

- It is possible and reasonable to conduct bilateral injections while observing appropriate procedures and precautions.
- The second injection should be treated as a separate procedure within the same visit.
- Where possible, products should not be from the same batch.
- Extra care is required for patients who require bilateral injections at the first visit.

The Viewpoint ‘Bilateral anti-VEGF treatment’ can be downloaded from: [https://www.visionacademy.org/resource-zone/patient-centric-care](https://www.visionacademy.org/resource-zone/patient-centric-care)

VEGF, vascular endothelial growth factor.
Further considerations

When extending treatment intervals, the needs of each eye should be considered separately, as the ideal treatment interval for one eye may be different to the fellow eye.

To reduce clinic burden, it may be preferable to treat both eyes according to the needs of the eye that requires the shortest interval. As such, the physician may risk over-treating one eye, but avoids undertreating the fellow eye, thus minimizing the risk of avoidable vision loss.

Additional larger studies are required to support the safety and efficacy of bilateral anti-VEGF therapies to enable payers to make informed choices about whether to reimburse treatment in countries where bilateral injection procedures are not, or only partially, reimbursed.

VEGF, vascular endothelial growth factor.