Anti-VEGF Optic Neuropathy (AVON)

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Financial Disclosure

- None
Summary

- Case Presentation
- Anti-VEGF Optic Neuropathy (AVON) Study
- Review Possible Mechanisms of IVI and POAG
- Learning Points and Considerations
Case Vignette:

Ms EB

- June 30, 2018
- 20/200 OD  CF OS
- Started Induction course of IVB
Case Vignette:

Ms EB

- Sept 25, 2019
- IVB x 1
- IVR x 8 (prn dosing)

- 20/70 OD  CF OS
- IOP 17 OD 16 OS
Case Vignette:

Ms EB

- Increased c/d from 0.3 to 0.5
Case Vignette:

Ms EB

- Increased c/d from 0.3 to 0.5
- Progressive thinning of NFL
Case Vignette:

Ms EB

- Increased c/d from 0.3 to 0.5
- Progressive thinning of NFL
- Glaucomatous VF changes
Case Vignette:

Ms EB

- Increased c/d from 0.3 to 0.5
- Progressive thinning of NFL
- Glaucomatous VF changes
- Tmax = 23
AVON Study

- IRB approval for retrospective consecutive case control trial

- 514 consecutive pts with anti-VEGF injections for DME or nAMD
- 271 matched pts with no prior injections with dx of NPDR or “dry” AMD

<table>
<thead>
<tr>
<th>Patient/Eye Status</th>
<th>Control Group</th>
<th>Study Group</th>
<th>Grand Total</th>
<th>Control Group</th>
<th>Study Group</th>
<th>Grand Total</th>
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</thead>
<tbody>
<tr>
<td>Initial patient/eye</td>
<td>304</td>
<td>624</td>
<td>928</td>
<td>608</td>
<td>908</td>
<td>1516</td>
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<td>population</td>
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<tr>
<td>Removed - Prior anti-</td>
<td>18</td>
<td>0</td>
<td>18</td>
<td>36</td>
<td>0</td>
<td>36</td>
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<tr>
<td>Removed - RVO</td>
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<td>72</td>
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<td>10</td>
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<tr>
<td>Removed – Prior Steroids</td>
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<td>18</td>
<td>18</td>
<td>0</td>
<td>29</td>
<td>29</td>
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<tr>
<td>Removed - Testing</td>
<td>10</td>
<td>19</td>
<td>29</td>
<td>20</td>
<td>24</td>
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<td>Unreliable</td>
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<tr>
<td>Removed – Prior</td>
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<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
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<td>Vitrectomy</td>
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<tr>
<td>Total patients included</td>
<td><strong>271</strong></td>
<td><strong>514</strong></td>
<td><strong>785</strong></td>
<td><strong>542</strong></td>
<td><strong>770</strong></td>
<td><strong>1312</strong></td>
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</table>
AVON Study: Demographics

- Gender
  - Control: 51% Female
  - Study: 53% Female

- Age

Patient Age Between Groups
AVON Study: Results

Glaucoma Status of Study vs. Control Group

- Control Group
- Study Patient

Number of patients

<table>
<thead>
<tr>
<th>Glaucoma Status</th>
<th>Study Patient</th>
<th>Control Group</th>
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</thead>
<tbody>
<tr>
<td>Glaucoma Dx</td>
<td>10</td>
<td>63</td>
</tr>
<tr>
<td>No Glaucoma</td>
<td>225</td>
<td>355</td>
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<tr>
<td>Suspect</td>
<td>36</td>
<td>96</td>
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</table>
AVON Study: Results

Glaucoma Status of Study vs. Control Group

- **No Glaucoma**
  - Study Patient: 355
  - Control Group: 225
  - **P<0.0001**

- **Suspect**
  - Study Patient: 36
  - Control Group: 96
  - **P<0.05**

**Number of patients**

- Glaucoma Dx: Study Patient 10, Control Group 63
AVON Study: Results

Mean IOP

- Control 19mm/Hg
- Study 26mm/Hg
AVON Study: Results

Mean IOP

- Control 19mm/Hg
- Study 26mm/Hg

Comparison of Ocular Hypertension with Anti-VEGF

Patient Population

P<0.00001
AVON Study: Results

Association of Glaucoma with IVI

- $R^2 = 0.857$
- $P < 0.01$

Percentage of Glaucoma vs. Mean Number of IVI
AVON Study: Results

Association of Ocular Hypertension with IVI

- $R^2 = 0.749$
- $P < 0.05$
Do Anti-VEGF injections cause COAG?


Conventional theories for COAG and injections:

1) Transient IOP elevation

2) Reduced facility of outflow
Conventional theories for COAG and injections:

Problem with these “theories” for anti-VEGF injections:

Multiple repeated injections of intravitreal ganciclovir did NOT result in IOP elevation/COAG**

**Personal communication with Dan Martin MD.
Conventional theories for COAG and injections:
Conventional theories for COAG and injections:

Is it possible for the medications to cause optic nerve abn \textit{outside of glaucoma}?
Diffusion abnormalities of the corpus callosum in patients receiving bevacizumab for malignant brain tumors: Suspected treatment toxicity

Article in Journal of Neuro-Oncology 118(1) · February 2014 with 21 Reads
DOI: 10.1007/s11555-014-1409-3 · Source: PubMed

Stephen F Futterer
Alexander J Nemeth
Sean Grimm
Ann B Ragin

Abstract

Bevacizumab has been reported to cause diffusion restriction in the tumor bed of patients with malignant gliomas. This study evaluated prolonged diffusion restriction, in the corpus callosum (CC), of patients with malignant brain tumors treated with bevacizumab. We retrospectively reviewed our database of patients treated with bevacizumab for malignant brain tumors looking for those with restricted diffusion in the CC. CC ADC ratio measurements were obtained prior to and following treatment. Correlation was made with biopsy (n = 3) and MR perfusion (n = 7) and PET (n = 4).

The temporal evolution of these changes relative to therapy was examined with mixed effects regression analysis. Nine patients (eight malignant gliomas, one malignant meningioma) out of 146 patients were found to have developed areas of diffusion restriction in the CC. These areas tended to enlarge and coalesce over serial MRIs and persisted for up to 22 months. Hypoperfusion was demonstrated in MR perfusion in 7/7. PET was hypometabolic in all 4. Biopsy of the CC showed no tumor in 3/3. ADC ratio measurements indicated a significant overall effect of time (F(16,60) = 11.2; p < 0.0001), consistent with persistent diffusion restriction over the measured time periods. Bevacizumab causes prolonged diffusion restriction in the CC. The negative MR perfusion, FDG PET and histopathology suggest this is a toxicity of bevacizumab and not active tumor. Awareness of these changes can assist in patient care.
Cardiovascular Adverse Events in Patients With Cancer Treated With Bevacizumab: A Meta-Analysis of More Than 20 000 Patients

Matthias Totzeck, Raluca Ileana Mincu, and Tienush Rassaf

Originally published 10 Aug 2017 [https://doi.org/10.1161/JAHA.117.006278] Journal of the American Heart Association. 6:e006278

Abstract

Background
The monoclonal antibody bevacizumab effectively inhibits angiogenesis in several types of cancers by blocking vascular endothelial growth factor. However, life-threatening cardiovascular adverse effects could limit its use and may warrant specific follow-up strategies.

Methods and Results
We systematically searched MEDLINE, Cochrane, EMBASE, and Web of Science for randomized controlled trials published until November 2016 that assessed patients with cancer treated with or without bevacizumab in addition to standard chemotherapy. A total of 20 050 patients with a broad range of cancer types from 22 studies were included in this analysis (10 394 in the bevacizumab group and 9656 in the control group). The risks of arterial and venous adverse events were higher in the bevacizumab groups (relative risk [RR], 1.37; 95% CI, 1.10–1.70 [P=0.004] and RR, 1.29; 95% CI, 1.12–1.47 [P<0.001], respectively), and more arterial adverse events occurred in patients taking high-dose bevacizumab regimens. Bevacizumab treatment was associated with the highest risk of cardiac and cerebral ischemia in the high-dose bevacizumab groups (RR, 4.4; 95% CI, 1.59–12.70 [P=0.004] and RR, 6.67; 95% CI, 2.17–20.66 [P=0.001], respectively). In addition, the risk of bleeding and arterial hypertension were higher in the bevacizumab groups (RR, 2.74; 95% CI, 2.38–3.15 [P<0.001] and RR, 4.73; 95% CI, 4.15–5.39 [P<0.00001], respectively), with higher values for patients taking high-dose regimens.

Conclusions
Treatment with bevacizumab increases the risk of arterial adverse events, particularly cardiac and cerebral ischemia, venous adverse events, bleeding, and arterial hypertension. This risk is additionally increased with high doses of bevacizumab. Further studies should determine the appropriate options for cardio-oncology management.
Potential causes of optic neuropathy:

1) COAG caused by either transient iop elevation or reduced facility of outflow (silicone droplets/particulate matter)

2) Vascular compromise from anti-VEGF mechanisms
AVON Case - Control Retrospective review:

-28/96 (29%) Glaucoma suspect pts never had iop > 22
-17/28 (61%) RNFL thinning
-11/17 (65%) had RNFL thinning with C/D .5 or >
Summary of Optic neuropathies in antiVEGF inj:

63/514 had glaucoma = 12.25%, P<0.0001

311/514 had iop elevation at some point = 60.50%, P<0.0001

96/514 had dx of glaucoma suspect = 18.67%, P<0.05

17/514 had low pressures but ipsilateral progression of cupping = 3.3%

** 3.3% of pts had progressive cupping with NO IOP elevation**
Premise behind Low Tension Glaucoma:

Research should now concentrate on evaluating these mechanisms that produce disc damage and field defects in all glaucomas. Our interests should be directed to the biology of the collagens and other building blocks of the optic nerve head; the possible local vascular or systemic vascular events; and other metabolic, systemic, and genetic factors that may determine the susceptibility of a nerve to develop the disease.

The existence of glaucoma with normal intraocular pressure and its relatively common occurrence has provided an incentive and an opportunity to reexamine our fundamental concepts of glaucoma damage. The whole spectrum of optic neuropathies with excavation should now be examined with epidemiologic, anatomic, and biochemical tools to identify the pathophysiology and the many factors that interact in the production of the characteristic clinical picture of this disease and its progression. Such reexamination will allow a rational approach to therapy for the disease, which will always include pressure reduction, because it is surely one of the noxious factors in glaucoma.

STEPHEN M. DRANCE, MD
Vancouver, British Columbia
AVON Syndrome:

1) Progressive optic nerve damage (cupping with VF and OCT NFL loss)
AVON Syndrome:

1) Progressive optic nerve damage (cupping with VF and OCT NFL loss)

2) In the absence of IOP elevation
AVON Syndrome:

1) Progressive optic nerve damage (cupping with VF and OCT NFL loss)

2) In the absence of IOP elevation

3) Possibility association of local vascular perfusion deficits
Learnings and considerations:

1) Enhanced Informed consent on all pts undergoing Anti-VEGF injections

2) Obtain OCT NFL on ALL pts getting anti VEGF injections

3) Hypervigilance of optic disc cupping changes
Learnings and considerations:

1) Enhanced Informed consent on all pts undergoing Anti-VEGF injections

2) Obtain OCT NFL on ALL pts getting anti-VEGF injections

3) Hypervigilance of optic disc cupping changes

4) Questions remain about longer term exposure to anti-VEGF agents that we are still potentially not aware of.