## 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



### Ms EB

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





### Ms EB

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

- 20/70 OD CF OS
- IOP 17 OD 16 OS





#### Ms EB

Increased c/d from 0.3 to 0.5



Sept 25, 2019





#### Ms EB

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



#### Aug 16, 2018

Asymmetry OD - OS

OD

#### Sept 25, 2019





### Ms EB

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





### 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

	population			population		
Patient/Eye Status	Control Group	Study Group	Grand Total	Control Group	Study Group	Grand Total
Initial patient/eye population	304	624	928	608	908	1516
Removed - Prior anti- VEGF Inj	18	0	18	36	0	36
Removed - RVO	5	72	77	10	83	93
Removed – Prior Steroids	0	18	18	0	29	29
Removed - Testing Unreliable	10	19	29	20	24	44
Removed – Prior Vitrectomy	0	1	1	0	2	2
Total patients included	271	514	785	542	770	1312

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## **AVON Study: Demographics**

- Gender

Age

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







Glaucoma Status of Study vs. Control Group





Glaucoma Status of Study vs. Control Group





Mean IOP

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





■ Control Group ■ Study Patient



Mean IOP

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





■ Control Group ■ Study Patient





Association of Glaucoma with IVI

Mean Number of IVI



Association of Ocular Hypertension with IVI





## Do Anti-VEGF injections cause COAG?

- Yannuzzi NA, Patel SN, Bhavsar KV, Sugiguchi F, **Freund KB**. Predictors of sustained intraocular pressure elevation in eyes receiving intravitreal anti-vascular endothelial growth factor therapy. *Am J Ophthalmol.* 2014;158(2):319-327.e2.
- Dedania VS, Bakri SJ. Sustained elevation of intraocular pressure after intravitreal anti-VEGF agents:
   What is the evidence? Retina 2015 May 35(5) 841-58
- Tseng jj, Vance SK, Della Torre KE, Mendonca LS, Cooney MJ, Klancnik JM, Sorenson JA, Freund KB.
   Sustained increased intraocular pressure related to intravitreal antivascular endothelial growth factor therapy for neovascular age-related macular degeneration. J Glaucoma 2012 Apri-May 21(4) 241-7.



1) Transient iop elevation





2) Reduced facility of outflow





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.











Is it possible for the medications to cause optic nerve abn 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/s11080-014-1409-2 - Source: PubMed
Cite this publication



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#### 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*<0.0001], 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.

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### Potential causes of optic neuropathy:

- 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 >



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## Summary of 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:





may also be interrelated.

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.

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## 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.





