Non Arteritic Ischemic Optic Neuropathy (NAION) and Avastin

Shalom Kelman, MD
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Anterior Ischemic Optic Neuropathy

- Acute, painless, visual loss, associated with visual field defects, optic disc swelling and peripapillary hemorrhages
- Pathology- Infarction of the optic nerve head
The Ischemic Optic Neuropathy Decompression Trial (IONDT)
Demographics

- No gender predilection
- 2.3-10.3 per 100,000 in the United States
- Average age 55 to 65 years
- 60% have one of the risk factors associated with small-vessel occulsive cerebrovascular disease
  - hypertension
  - diabetes mellitus
  - cigarette use
Symptoms

- Blurred vision, loss of visual field
- Painless
- Initial visual acuity
  - 1/2 better than 20/64, while 1/3 worse than 20/200.
  - younger than 65 years better visual acuity
  - progression 1/3 of patients
Final Vision (6 Months)

- 1/2 final visual acuity of 20/200 or worse
- Spontaneous improvement of three or more lines of vision 42%
IONDT Follow-up Study

- Second eye involvement
- Prior to IONDT reported 40%
- IONDT found 15% over 5 years
Fundus

- Swollen optic disc - diffuse or focal
- Flame shaped hemorrhages
- Fellow eye exhibits “disc at risk” appearance
Necessary but not Sufficient

“Disc at risk” is necessary for development of NAION
  – 90% of NAION patients have it

But, is not sufficient
  – Of patients with “Disc at risk” appearance very few develop NAION
Fluorescein angiography

- Delayed optic disc filling
- No delay in adjacent peripapillary choroidal filling.
- Arteritic ION - marked delays in choroidal appearance and filling
Fundus in Arteritic ION

- Optic disc milky or pale swelling
- Cotton wool spots
- Optic discs may be of any size

Clinical Pearl
- Fellow eye normal disc - suspect GCA
Pathogenesis of NAION

- Vascular insufficiency producing optic nerve head ischemia
  - Autoregulation dysfunction
- Abrupt onset of vision loss
- Lack of ocular inflammation
Pathogenesis

- Venous congestion hypothesis of Levin and Danesh-Meyer
- Closure of tributary venules that receive blood from optic nerve head capillaries and drain into CRV
- **Vasogenic edema primary effect**
- In contrast, cytotoxic edema is primary consequence of arterial infarction

Pathogenesis of Arteritic ION

- Inflammatory occlusion of the short posterior ciliary arteries
- Retrobulbar ION - interruption of blood flow to retrolaminar region
Disc Morphology

- NAION
  - crowded, small disc
  - disc morphology does not change

- Arteritic ION
  - normal variation in cup size
  - Progressive cupping due to global ischemia and effacement of disc architecture
Intravitreal Bevacizumab for Nonarteritic Anterior Ischemic Optic Neuropathy

A Pilot Study

Shalom Kelman
Michael Elman
Naresh Mandava
Jeffrey Bennett
VEGF

Vascular Endothelial Growth Factor
• Signaling protein
• Stimulates angiogenesis
• Increases microvascular permeability
  – Increases leakage
The Use of Anti-VEGF

Intravitreal anti-VEGF injections
Bevacizumab, Avastin®
Ranibizumab, Lucentis®

Specifically found effective in
- Reducing angiogenesis in CNV and ROP
- Reducing macular edema in DME / CRVO
  - Reduces vascular leakage
Hypothesis

- VEGF signaling from ischemic tissue results in a rapid increase in vascular permeability
- Tight compartment syndrome – cycles of edema and ischemia leading to infarction
- VEGF inhibition of vasogenic edema could break the cycle and reduce ischemia
Pathogenesis

- Venous congestion hypothesis of Levin and Danesh-Meyer
- Closure of tributary venules that receive blood from optic nerve head capillaries and drain into CRV
- Vasogenic edema primary effect

Background

- Bennett et al case report
- Marked improvement in NFL edema and visual function after single injection of intravitreal bevacizumab in one case of NAION
Before 9d after Avastin injection

Is Avastin reducing the vasogenic edema of the ONH?

Purpose

- Evaluate drug safety and study feasibility
- Assess the effect on visual acuity
Methods

- Retrospective chart review
- Patients offered off-label treatment
- Initially only offered if VA poor, later even for 20/20 eyes
- Intravitreal injection of 1.25 mg/0.05 mL bevacizumab administered by experienced retina specialist
Results

- 30 eyes with acute NAION within 16 months
- 26 eyes (87%) were injected within 14 days of onset
- No cases of endophthalmitis or complications from injection
Baseline visual acuity ranged 20/20 to CF
ETDRS refracted visual acuities available on 20 of 30 eyes
ETDRS VA at 3 Months

- ETDRS acuity at baseline and 3 months available for 14 eyes
- 8/14 (57%) gained > 3 lines of vision
- 1/14 lost > 3 lines
Baseline VA < 20/64

- 6/8 (75%) gained >3 lines at 3 months
- IONDT 40% gained >3 lines at 3 months

Disc Edema

- Fundus photos demonstrated a rapid improvement (within 2 weeks) in disc edema in 15/20 (75%) eyes.
- Median time to spontaneous resolution of disc edema 8 weeks
  - (5.8 wks 25\textsuperscript{th} percentile -11.4 wks 75\textsuperscript{th} percentile)

Subfoveal Fluid

Hedges et al described 8/76 eyes with NAION studied with OCT

5/8 improved VA (2 lines) as fluid resolved in approximately 1 month

Hedges TR et al. Subretinal fluid from AION demonstrated by OCT. Arch Ophthalmol;2008;126:812-815
Subfoveal Fluid

- 4 eyes with subfoveal fluid
  - discrete area of hyporeflectivity under foveal region
- 4/5 gained >3 lines by 1 month
Conclusions

- Intravitreal bevacizumab for NAION appears safe and well tolerated
- 40% gain of significant visual acuity at 1 month points to rapidity of effect
- Correlates with observed rapid reduction in disc edema
Conclusions

- Early administration (87% within 2 wks) may contribute to effectiveness
  - May slow progression
  - May reverse visual loss
- Subgroup of patients with maculopathy may benefit from early treatment
- Findings support the proposed benefit of VEGF inhibition to reduce vasogenic edema and limit tissue damage in NAION
Does it Work?

- A randomized clinical trial of intravitreal bevacizumab in NAION is feasible and warranted.
- Subgroup with subfoveal fluid may have higher spontaneous improvement rate.
- Elucidation of mechanism in animal model is desirable.
Intravitreal Injection of Bevacizumab may be Neuroprotective in a Mouse Model of Optic Nerve Crush

Daniel Rappoport, 1
Dana Morzaev, 2,4 Shirel Weiss, 2,4 Mark Vieyra, 4 Hana Leiba 1,5 and Nitza Goldenberg-Cohen 2,3,4

1Ophthalmology Department, Kaplan Medical Center, Rehovot, Israel; 2The Pediatric Eye Research Laboratory, Felsenstein Medical Research Center, Tel Aviv University, Petah-Tiqwa, Israel; 3Pediatric Unit, Ophthalmology Department, Schneider Children’s Medical Center of Israel, Petah- Tiqwa, Israel; 4Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; 5Hadassah and Hebrew University Medical School, Jerusalem, Israel.

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