Occlusive retinal vasculitis following intravitreal brolucizumab for exudative AMD

Retina Society – Annual Meeting 2020

Andre J Witkin MD
on behalf of the ASRS ReST Committee
Relevant Financial Disclosures

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  Allergan – Consultant
  Novartis – Investigator
  Genentech – Investigator

See program for full disclosure of the ASRS ReST Committee
Summary

- 26 eyes of 25 patients with retinal vasculitis after brolucizumab reported to ASRS
- Most (88%) were female
- Most (92%) had intraocular inflammation
- Most (88%) had retinal vascular occlusion
- Nearly half (46%) had significant visual loss (>3 lines)
ASRS ReST Committee

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- Andre J Witkin, MD
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Brolucizumab

• Single chain antibody fragment, blocks all VEGF-A
• Higher molar equivalent dose than other drugs:
  – Low molecular weight
  – High solubility
• FDA approval for exudative AMD: October 7, 2019
Brolucizumab

• After FDA approval, ASRS began receiving reports of retinal vasculitis after brolucizumab

• Study Purpose:
  – To describe clinical and imaging characteristics of these cases
Methods

• ASRS collected reports of retinal vasculitis after brolucizumab between 10-7-20 and 4-1-20
• ASRS sent standardized questionnaire to submitting physicians
• Data/images collected and analyzed by ASRS ReST Committee
Case example 1

72-year-old woman

• 30 prior anti-VEGF injections
• Received brolucizumab x3
• VA at each brolucizumab was 20/50

Courtesy of April Harris MD
Case example 1

72-year-old woman

- 63 days after brolucizumab #3, routine f/u
- Asymptomatic

Courtesy of April Harris MD
Case example 2

92-year-old woman

- 65 prior anti-VEGF injections
- Received brolucizumab x1
- VA at brolucizumab was 20/60
Case example 2

92-year-old woman

• 14 days after brolucizumab #1
  – **Symptoms:** redness, pain, and blurry vision
  – **Exam:** VA 20/100, Trace AC cells and KP
  – **Treatment:** Topical steroids

• 24 days after brolucizumab #1
  – **Symptoms:** Pain improved but vision worse
  – **Exam:** VA CF 4’, vitritis, arterial sheathing and retinal whitening

Courtesy of Elizabeth Verner-Cole MD
Case example 2

92-year-old woman

• VA CF 4’
Case example 2

92-year-old woman

• **Treatment:** Oral prednisone 60mg initiated

• 10 days after PO prednisone initiation (34 days after brolucizumab #1)
  – **Exam:** Retinal whitening improving, VA remained CF 4’
Case example 3

78-year-old man

- 59 prior anti-VEGF injections
- Received brolucizumab x1
- VA at brolucizumab was 20/60

Courtesy of Sachin Mehta MD
Case example 3

78-year-old man

• 14 days after brolucizumab
  – Saw general ophtho, diagnosed “uveitis”
  – Treatment: Topical steroids

• 35 days after brolucizumab
  – Symptoms: Blurry vision, floaters, pain, redness
  – Exam: VA HM, 2+ AC cells, vitritis, occlusive retinal vasculitis
  – Treatment: Oral prednisone

Courtesy of Sachin Mehta MD
Case example 3

78-year-old man

- VA HM

Courtesy of Sachin Mehta MD
Demographics

• 25 patients, 26 eyes
• Age: 58 – 92 years (mean 79)
• Sex: 22 women (88%), 3 men (12%)
• Prior treatment: All had prior anti-VEGF
  – Mean 39 injections (range 2-78)
  – 16% ranibizumab, 23% bevacizumab, 61% aflibercept
  – Reason to switch: 77% extend interval, 73% improve anti-VEGF efficacy
Brolucizumab injections

- Vasculitis occurred following:
  - 1 injection – 42%
  - 2 injections – 42%
  - 3 injections – 16%

- No associated lot (10 reported lot numbers)
Symptoms

- Blurry vision – 62%
- Floaters – 46%
- Pain – 31%
- Redness – 19%
- Scotomas – 12%
- Asymptomatic – 8%
Exam Findings

• Inflammation (other than vasculitis) noted in 92%
  – Anterior only – 31%
  – Posterior only – 27%
  – Both – 35%
  – None – 8%

• Vascular occlusion noted by referring physician in 85%
  – 6 eyes first presented with inflammation, subsequently developed vascular occlusion
Vasculitis Features

• Images available from 24/26 eyes (92%)
  – Color photos – 24 (92%)
  – FA – 22 (85%), ICG – 1 (4%)
  – OCT – 18 (69%)

• Imaging features (ischemia evident in 88%)
  – Arterial involvement – 91%
  – Venous involvement – 79%
  – Choroidal hypoperfusion - 48%
  – Optic nerve hyperfluorescence – 55%
## VA Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Mean Snellen VA</th>
<th>Median Snellen VA</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>VA at most recent brolucizumab <em>(baseline)</em></td>
<td>20/52</td>
<td>20/50</td>
<td>20/25 – 4/200</td>
</tr>
<tr>
<td>VA at Adverse Event (AE) onset</td>
<td>20/151</td>
<td>20/70</td>
<td>20/25 – HM</td>
</tr>
<tr>
<td>Worst VA</td>
<td>20/397</td>
<td>20/150</td>
<td>20/30 – LP</td>
</tr>
<tr>
<td>VA at most recent follow-up</td>
<td>20/243</td>
<td>20/80</td>
<td>20/30 – LP</td>
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<td><em>(Mean 53 days since last brolucizumab)</em></td>
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46% with ≥ 3-line VA loss at last follow-up
Treatment

- No consistent pattern of response
- 8 eyes re-treated with another anti-VEGF
  - 4 had no inflammation at injection, and no recurrence
  - 2 had inflammation at injection, and no recurrence
  - 2 had inflammation at injection, and worse inflammation
Epidemiology

• More common in women (88%)
  – Could be by chance

• High rate of intraocular inflammation with brolucizumab
  – Data from independent SRC review commissioned by Novartis
    • 4.6% intraocular inflammation
    • 3.3% retinal vasculitis
    • 2.1% retinal vasculitis and occlusion

Etiology

• Data from FDA review of brolucizumab
  – High baseline rate of anti-drug antibodies (36-52%)
  – High rate of induced or boosted ADA levels (23-25%)
    • Associated with higher risk of inflammation
      https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761125Orig1s000SumR.pdf
      https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761125s000lbl.pdf

• More potent anti-VEGF effect may reach threshold to induce retinal vascular occlusion
Recommendations

- Informed consent when using brolucizumab should include discussion of retinal vasculitis and associated vision loss
- Careful exam for inflammation prior to every brolucizumab
- Angiography helpful to analyze spectrum of vasculopathy
- Ideally, re-treat with anti-VEGF once inflammation resolves
Thank you to all those that contributed data for this study!

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