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

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

Relevant Financial Disclosures

Andre J Witkin MD

- Allergan – Consultant
- Novartis – Investigator
- Genentech – Investigator

See program for full disclosure of the ASRS ReST Committee

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

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)

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

ASRS ReST Committee

- Timothy G Murray, MD MBA FACS (President, ASRS)
- Paul Hahn, MD PhD (Chair, ASRS ReST Committee)

- J Fernando Arevalo, MD PhD FACS
- Kevin J Blinder, MD
- Netan Choudhry, MD FRCSC
- Roger A Goldberg, MD MBA
- Joel Pearlman, MD PhD
- Eric W Schneider, MD
- Stephen J Kim, MD
- Homayoun Tabandeh, MD MS
- Andre J Witkin, MD
- Robert W Wong, MD

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

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

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

Brolucizumab

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

- Study Purpose:
  - To describe clinical and imaging characteristics of these cases

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

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

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

Case example 1

72-year-old woman

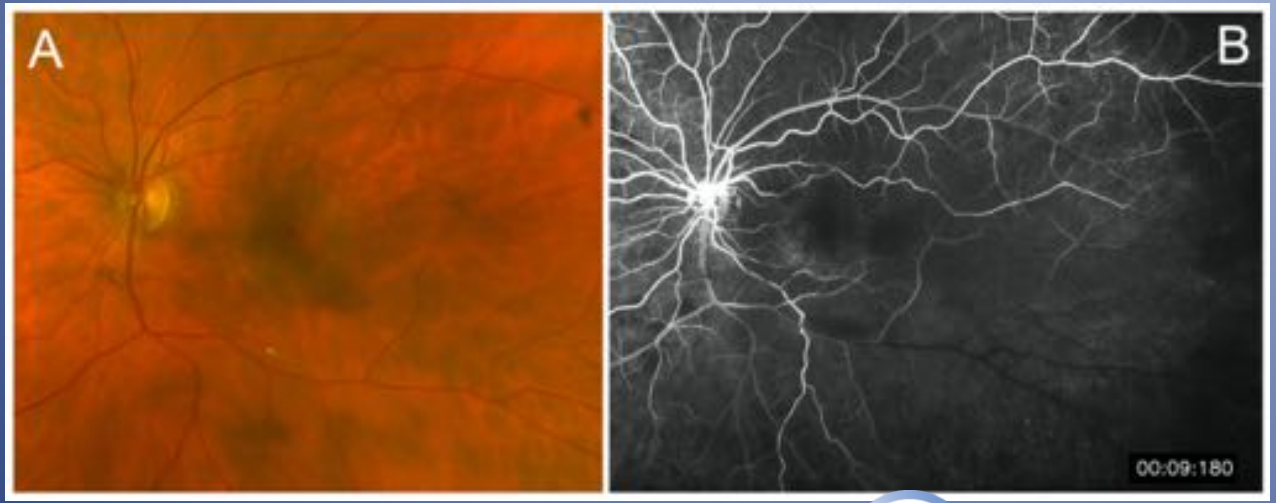
- 30 prior anti-VEGF injections
- Received brolucizumab x3
- VA at each brolucizumab was 20/50

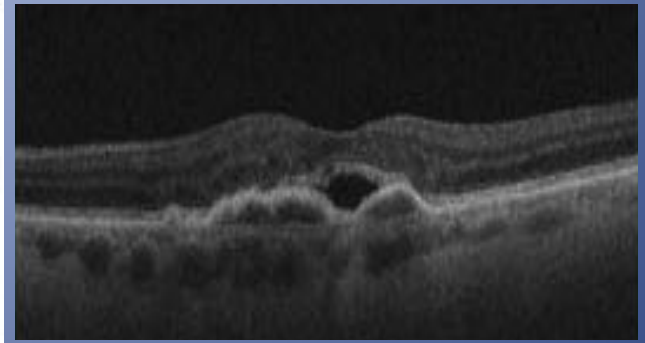
Courtesy of April Harris MD

Case example 1

72-year-old woman

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





Courtesy of April Harris MD

ASRS American Society of Retina Specialists

Case example 2

92-year-old woman

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

Courtesy of Elizabeth Verner-Cole MD

ASRS American Society of Retina Specialists

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

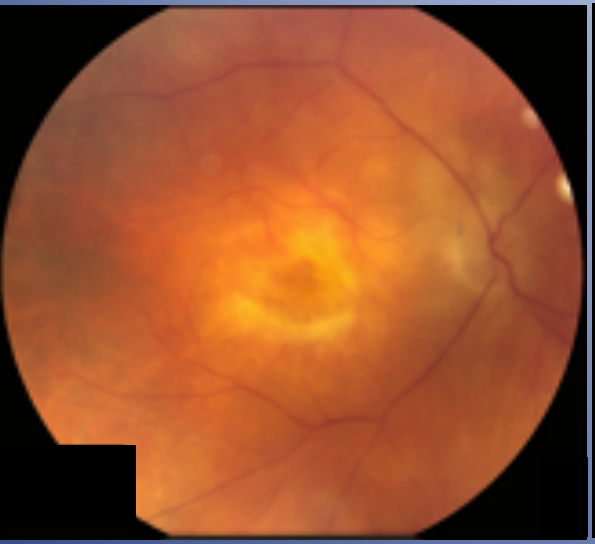
Courtesy of Elizabeth Verner-Cole MD

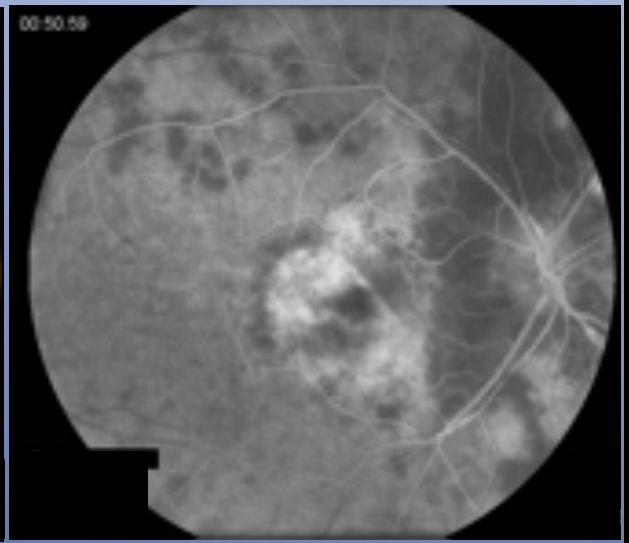
ASRS American Society of Retina Specialists

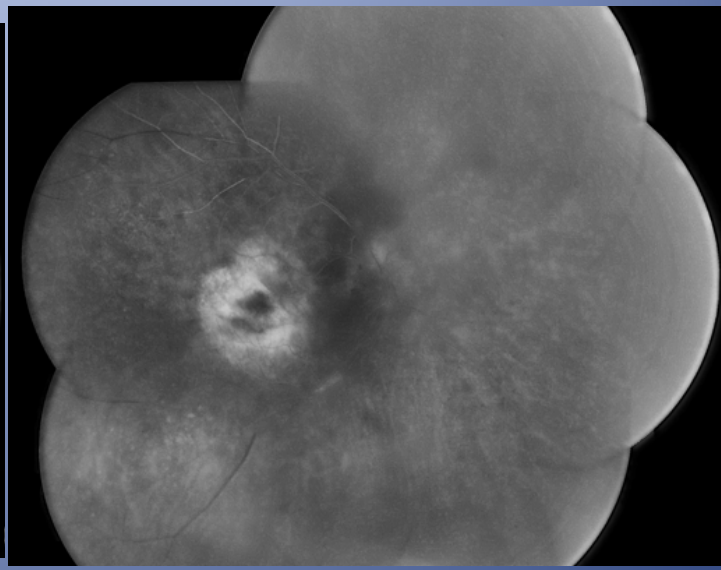
Case example 2

92-year-old woman

- VA CF 4’







Courtesy of Elizabeth Verner-Cole MD

ASRS American Society of Retina Specialists

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’

Courtesy of Elizabeth Verner-Cole MD

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

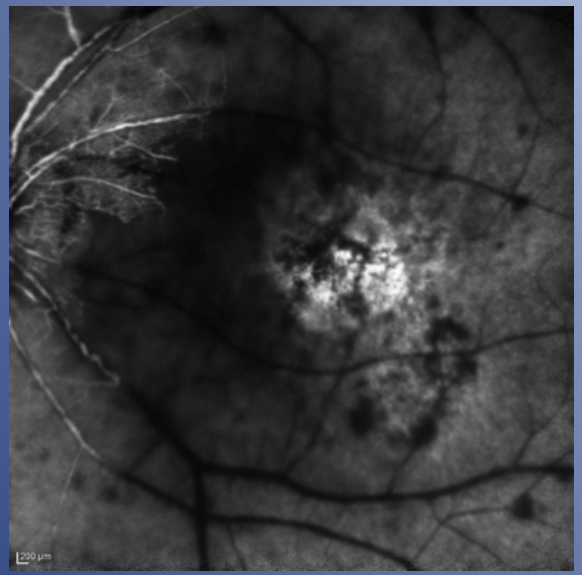
Courtesy of Sachin Mehta MD

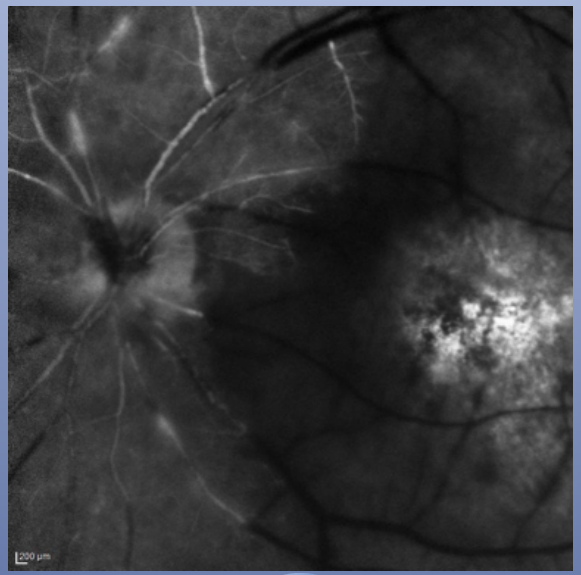
ASRS American Society of Retina Specialists

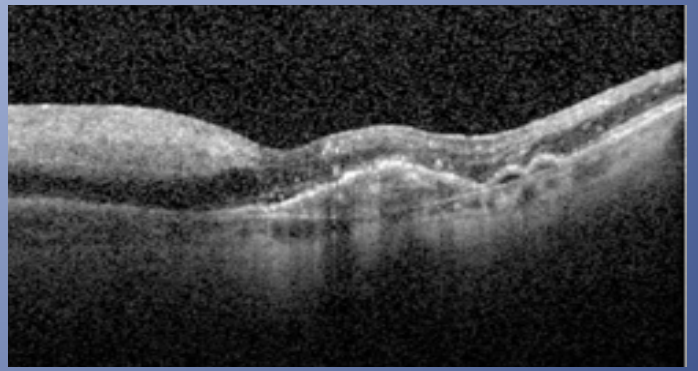
Case example 3

78-year-old man

- VA HM







Courtesy of Sachin Mehta MD

ASRS American Society of Retina Specialists

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

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

Brolucizumab injections

- Vasculitis occurred following:
  - 1 injection – 42%
  - 2 injections – 42%
  - 3 injections – 16%
- No associated lot (10 reported lot numbers)

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

Symptoms

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

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

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

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

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%

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

VA Outcomes

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

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

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

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

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

https://www.brolucizumab.info/dist/files/ASRS_SRC_report.pdf

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

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

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

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

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists

Thank you to all those that contributed data for this study!

- Mark E. Chittum
- Matthew Dombrow
- Kori Elkins
- K. Bailey Freund
- Paul Gallogly
- April Harris
- Vishak John
- Srinivas Sai Kondapalli
- Rohit Lakhanpal
- Mattew Manry
- Sachin Mehta
- Patrick Oellers
- Marc Peden
- Ryan Rich
- Jason Paul Ruggiero
- Bryan Rutledge
- Newman Sund
- Elizabeth Verner-Cole
- Scott Walter
- Mark Walsh
- John Welch
- Steve Witkin
- Matthew Wood

Research & Safety in Therapeutics

ASRS American Society of Retina Specialists