An Update on Branch Retinal Vein Occlusion Treatment Studies

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Course Description

• This course focuses on current treatment options available for macular edema and neovascularization secondary to branch retinal vein occlusion (BRVO).
Course objectives

• Briefly review what vision threatening conditions can occur in patients with BRVO
• Understanding what treatment options are available to treat these vision threatening conditions secondary to BRVO
• Reviewing important research studies on these treatment options for BRVO
• Understand what treatment options are currently recommended and being employed for BRVO
Treatment: Introduction

• BRVO: What are we treating?
• Potential complications:
  • Macular edema $\rightarrow$ Vision loss
  • Retinal neovascularization $\rightarrow$ Retinal damage/detachment
  • Iris/angle neovascularization $\rightarrow$ Neovascular glaucoma
• Goal:
  • Eliminate macular edema
  • Eliminate retinal/iris/angle neovascularization
What are the options??
Systemic Treatment

• Medical treatment is **NOT** effective
  • Anticoagulants
  • Fibrinolytic agents
  • Clofibrate capsules (atromid-S)
  • Carbogen inhalation
  • Hemodilution
Ocular Treatments

• **Surgical care**
  • Macular grid laser photocoagulation
  • Scatter photocoagulation
  • Laser-induced chorioretinal anastomosis
  • Vitrectomy and arteriovenous decompression

• **Pharmacotherapy**
  • Intravitreal corticosteroid therapy
    • Triamcinolone (Kenalog-40)
    • Dexamethasone intravitreal implant (Ozurdex)
  • Intravitreal anti-VEGF
    • Bevacizumab (Avastin)
    • Ranibizumab (Lucentis)
    • Aflibercept (Eylea)
BRVO Studies

- BVOS – BRVO (landmark study)
- GENEVA – BRVO & CRVO
- SCORE – BRVO
- BRAVO – BRVO
- HORIZON – BRVO & CRVO
- VIBRANT – BRVO & hemi-RVO
- BERVOLT – BRVO & CRVO
- BRIGHTER – BRVO
- RELATE – BRVO & CRVO
BVOS

Branch Vein Occlusion Study
(Landmark study)
BVOS: Background

• Many treatments attempted before 1977 but none were effective
• Only treatment that seemed promising is laser photocoagulation
BVOS: The Basics

• **Branch Vein Occlusion Study (BVOS)** was a multi-center, prospective, randomized, controlled clinical trial supported by the National Eye Institute (NEI)

• **Date**: 1984 and 1986

• **Participants**: 540

• **Duration**: mean of 3.1 years
BVOS: Purpose

• The BVOS was designed to answer the following questions:

• 1. Can peripheral scatter argon laser photocoagulation prevent the development of neovascularization?

2. Can peripheral scatter argon laser photocoagulation prevent vitreous hemorrhage?

3. Can macular argon laser photocoagulation improve visual acuity in eyes with macular edema reducing vision to 20/40 or worse?
BVOS: Protocol

**Groups:**
- 1. Eyes with $\geq 5$DD nonperfusion w/o NV (319 eyes)
- 2. Eyes with NV (82 eyes)
- 3. Eyes with BRVO & ME & VA $\leq 20/40$ (139 eyes)

$\frac{1}{2}$ were randomly assigned to treatment with argon laser photocoagulation
$\frac{1}{2}$ remained untreated as controls
BVOS: Results

Summarized results:

• 1. Overall, 63% of nonperfused eyes will develop neovascularization
• 2. 31% of eyes develop vitreous hemorrhage after being treated for neovascularization and nonperfusion
• 3. Eyes randomized to grid laser had visual acuity gain
BVOS: Conclusion

Questions:
• 1. Can peripheral scatter argon laser photocoagulation prevent the development of neo-vascularization?
• 2. Can peripheral scatter argon laser photocoagulation prevent vitreous hemorrhage?
• 3. Can macular argon laser photocoagulation improve visual acuity in eyes with macular edema reducing vision to 20/40 or worse?

Conclusions:
• 1/2. Peripheral scatter argon laser photocoagulation PREVENTED of both neo-vascularization and vitreous hemorrhage to a significant degree.
  • Laser should be applied after, rather than before, the development of neo-vascularization.
• 3. Argon laser photocoagulation improved the VA to a significant degree in eyes with BRVO and visual acuity reduced from macular edema to 20/40 or worse.
  • Recommended laser for patients with macular edema
BVOS: Prognosis

• Good
• 50% have >20/40 vision unless foveal ischemia or chronic macular edema is present
• Risk of another BRVO in same eye is 3% and in fellow eye is 12%
SCORE

The Standard Care vs. Corticosteroid for Retinal Vein Occlusion Study
SCORE: The Basics

- The Standard Care vs. Corticosteroid for Retinal Vein Occlusion Study
- Start date: November 2004
- Complete date: February 2008
- Participants: 411
- Duration: 12 months
SCORE: PURPOSE

- **Purpose**: To assess the efficacy and safety of standard care (grid laser) vs. triamcinolone acetonide injections (1mg and 4mg doses) for the treatment of macular edema associated with CRVO and BRVO
SCORE: Protocol

• Groups:
  • 1. IV triamcinolone (1mg)
  • 2. IV triamcinolone (4mg)
  • 3. Standard care (macular grid laser):
    • CRVO: observation
    • BRVO:
      • Grid photocoagulation w/o dense macular heme
      • Deferral of photocoagulation w/ dense macular heme until clear
SCORE: Results

• Compare
  • 4mg triamcinolone vs standard care
  • 1mg triamcinolone vs standard care
  • 4mg vs 1 mg triamcinolone

at 1 year:

<table>
<thead>
<tr>
<th>Change in VA letter score</th>
<th>SC</th>
<th>1 mg</th>
<th>4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 15 gain</td>
<td>29%</td>
<td>26%</td>
<td>27%</td>
</tr>
</tbody>
</table>

significantly higher ocular complications
SCORE: Results

• Higher ocular complications with 4mg triamcinolone acetonide injections:
  • Elevated intraocular pressure
  • Cataract formation

• Overall complications with corticosteroid use:
  • Cataract formation
  • Elevation of IOP
  • Infectious endophthalmitis
  • Non-infectious endophthalmitis
  • Retinal detachment
SCORE: Conclusion

• **VA**: No significant difference at 12 months
  • 12-36months: **SC group** had best VA improvement
• **OCT retinal thickness**: All 3 groups had reduction from baseline to 12 months
  • 12-36months: **SC group** had greatest reduction
• **SC group** had a better **safety** profile than triamcinolone group
• **Conclusion**: SC (grid laser) better for Tx of macular edema secondary to BRVO
• *For both CRVO and BRVO:*
  • Younger age = improved VA and central retinal thickness
  • Shorter duration of macular edema = better outcome
Other corticosteroids?

- **SCORE**: tested Triamcinolone
- **Dexamethasone**
  - More potent
  - Intravitreal injections:
    - High drug levels
    - Without toxic effects
- **Downfall**:
  - Short intraocular life ~3 hours
- **Ozurdex** (dexamethasone implant):
  - Lasts ~4 months
  - Designed and approved for ME 2/2 vein occlusion
BRAVO

Ranibizumab (Lucentis) for the Treatment of Macular Edema following BRAch Retinal Vein Occlusion
BRAVO: THE BASICS

• **Ranibizumab** for the Treatment of Macular Edema following **BRAch Retinal Vein Occlusion**

• **Start date**: July 2007
• **End date**: May 2009
• **Duration**: 12 months
• **Participants**: 397
BRAVO: Purpose

• **Purpose:** to study the efficacy and safety of IV ranibizumab (anti-VEGF) 0.3mg & 0.5mg vs sham (placebo) injections in patients with macular edema secondary to BRVO
BRAVO: Protocol

3 groups

Treatment: 1\textsuperscript{st} 6 months
- 1. Sham injection (control)
- 2. 0.3 mg ranibizumab IV injection q1m
- 3. 0.5 mg ranibizumab IV injection q1m

Observation: 2\textsuperscript{nd} 6 months
- Patients assessed monthly
- Ranibizumab PRN if:
  - Vision ≤ 20/40 or
  - OCT central thickness ≥ 250

- Rescue grid laser photocoagulation offered at 3 and 9 months if specific criteria is met
## BRAVO: Results

### Letter Gain

<table>
<thead>
<tr>
<th></th>
<th>Treatment: 1(^{st}) 6 months</th>
<th>Observation: 2(^{nd}) 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham (control)</td>
<td>7.3 letters</td>
<td>12.1 letters</td>
</tr>
<tr>
<td>0.3mg ranibizumab</td>
<td>16.6 letters</td>
<td>16.4 letters</td>
</tr>
<tr>
<td>0.5mg ranibizumab</td>
<td>18.3 letters</td>
<td>18.3 letters</td>
</tr>
</tbody>
</table>

### % of patients gained 3 lines

<table>
<thead>
<tr>
<th></th>
<th>% of patients gained 3 lines</th>
<th>Needed rescue laser</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Overall</td>
</tr>
<tr>
<td>Sham (control)</td>
<td>28.8%</td>
<td>54.5%</td>
</tr>
<tr>
<td>0.3mg ranibizumab</td>
<td>55.2%</td>
<td>18.7%</td>
</tr>
<tr>
<td>0.5mg ranibizumab</td>
<td>61.1%</td>
<td>19.8%</td>
</tr>
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</table>
BRAVO: Conclusions

• Ranibizumab (0.3mg or 0.5mg) for 6 months caused rapid and sustained improvement in BCVA

• Ranibizumab shown to be effective in treating macular edema secondary to BRVO

• Good safety
  • Serious adverse effects and adverse effects rare

• Things to consider:
  • This study is ranibizumab vs placebo, not vs laser
VIBRANT

Intravitreal aflibercept (Eylea) for macular edema following branch retinal vein occlusion
VIBRANT: THE BASICS

• Intravitreal aflibercept (Eylea) for macular edema following branch retinal vein occlusion
• Start date: April 2012
• End date: March 2014
• Duration: 12 months
• Participants: 181
VIBRANT: Purpose

• **Purpose**: to determine efficacy and safety outcomes in eyes with ME after BRVO treated with 2mg IV aflibercept injection compared with grid laser
VIBRANT: Protocol

Randomized into TWO groups

**IV aflibercept injection**
- Injection q4 weeks through week 24
- Injection q8 weeks through week 48
- Rescue laser PRN week 36

**Laser photocoagulation**
- Grid laser at baseline
- If rescue needed: 1 additional laser week 12-20 and aflibercept injection q 8 weeks after 3 monthly doses from week 24 onward (laser/aflibercept group)
VIBRANT: Conclusions

• **Afibercept is an effective treatment for ME due to BRVO**

• After 6 monthly injections of afibercept, injections q8weeks maintained control of ME and VA benefits through week 52

• The VA benefits were significantly better in eyes treated with afibercept q4 weeks for 24 weeks vs treated with grid laser therapy

• In the laser group, rescue afibercept resulted in substantial VA improvements at week 52
BERVOLT

Bevacizumab (Avastin) for RVO Long-Term Follow Up
BERVOLT: The Basics

Bevacizumab for RVO Long-Term Follow Up

• Date: 2015
• Duration: mean follow up of 24.4 months
• Participants: 87 eyes (BRVO) & 65 CRVO
• Study type: Retrospective, non-comparative case series
Purpose: To assess the efficacy and safety of intravitreal injections of bevacizumab in patients with macular edema following BRVO and CRVO
BERVOLT: Protocol

• Retrospective, non-comparative case series

• **Inclusion:**
  • Patients ≥ 18 years old with ME secondary to BRVO or CRVO
  • Minimum of 1 IV bevacizumab injection
BERVOLT: Results

• **Results:**
  • Significant improvement of VA
  • Mean improvement of 13 letters at 2 years with average 7.6 injections
BERVOLT: Conclusion

• Bevacizumab is an alternative anti-VEGF therapy for ME secondary to BRVO
• VA gains are similar to findings in BRAVO study (Ranibizumab)
• Study limitations:
  • Retrospective, non-comparison case series
  • Lack randomization
  • Variable protocol use of bevacizumab (not standardized)
BRIGHTER

Individualized Stabilization Criteria-Driven Ranibizumab versus Laser in Branch Retinal Vein Occlusion

(6 month results)
BRIGHTER: The Basics

• Phase IIIb, randomized, open-label, active-controlled, 3 arm, multicenter study

• **Date**: published June 2016 (started May 2012)

• **Duration**: 6 months (projected 24 months)

• **Participants**: 455
BRIGHTER: Purpose

• **Purpose:** assessing the efficacy and safety profile PRN dosing regimen of ranibizumab 0.5mg alone or in combination with laser vs laser photocoagulation in patients with VA impairment due to ME secondary to BRVO

• **Questions:**
  • 1. Long term – efficacy and safety of ranibizumab 0.5mg in BRVO (w/ or w/o ME)
  • 2. Impact of adjunct laser Tx on VA and number of ranibizumab injections required
BRIGHTER: Protocol

• Three groups:
  • 1. Ranibizumab 0.5mg
  • 2. Ranibizumab 0.5mg with laser
  • 3. Laser alone
BRIGHTER: Conclusions

- 6 month data showed ranibizumab alone with or without laser is SUPERIOR to laser monotherapy in significantly improving VA in patients with BRVO
- *Similar VA gains between patients with macular ischemia vs patients w/o ischemia
  - Suggesting early treatment can improve VAs irrespective of baseline VA (seen as early as the 6 month mark)
RELATE

Ranibizumab DosE Comparision (0.5mg and 2.0mg) And the Role of LAser in the Management of Retinal Vein Occlusion
RELATE: The Basics

• RELATE: Ranibizumab Dose Comparison (0.5mg and 2.0mg) And the Role of Laser in the Management of Retinal Vein Occlusion
  • BRVO & CRVO
  • Purpose: to compare effects of 0.5mg or 2mg of ranibizumab q6months in patients with CRVO or BRVO
  • Protocol:
    • 6 sessions of monthly injections to both 2mg and 0.5mg
    • At 6 months: randomization to see if laser to areas with capillary nonperfusion can help resolve edema with less injections and if VAs are maintained despite laser treatment

• Results pending....
BRVO Studies Summary

• **BVOS – BRVO (landmark study):** laser ME and AFTER NV
• **GENEVA – BRVO & CRVO**
• **SCORE – BRVO:** Laser better for ME vs corticosteroids
• **BRAVO – BRVO:** Ranibizumab is effective for treating ME
• **HORIZON – BRVO & CRVO**
• **VIBRANT – BRVO & hemi-RVO:** Aflibercept is effective for treating ME
• **BERVOLT – BRVO & CRVO:** Bevacizumab is effective for treating ME
• **BRIGHTER – BRVO:** Ranibizumab (alone) w/ or w/o laser is better than laser alone for ME
• **RELATE – BRVO & CRVO:** 0.5mg vs 2mg Ranibizumab - Results pending
Treatment Summary

• BRVO: What are we treating?

• Potential complications:
  • Macular edema $\rightarrow$ Vision loss
  • Retinal neovascularization $\rightarrow$ Retinal damage/detachment
  • Iris/angle neovascularization $\rightarrow$ Neovascular glaucoma

• Goal:
  • Eliminate macular edema
  • Eliminate retinal/iris/angle neovascularization
Ocular Treatments Summary

• **Surgical care**
  - Macular grid laser photocoagulation
  - Scatter photocoagulation
  - Laser-induced chorioretinal anastomosis
  - Vitrectomy and arteriovenous decompression

• **Pharmacotherapy**
  - Intravitreal corticosteroid therapy
    - Triamcinolone (Kenalog-40)
    - Dexamethasone intravitreal implant (Ozurdex)
  - Intravitreal anti-VEGF
    - Bevacizumab (Avastin)
    - Ranibizumab (Lucentis)
    - Aflibercept (Eylea)
Thank you
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Question 1

What is(are) the goal(s) to treating patients with BRVO?

a) To eliminate macular edema and neovascularization
b) To decrease intraocular pressures spikes
c) To accelerate the clearing to retinal and/or vitreal hemorrhages
d) To investigate the systemic case and initiate systemic oral treatment
e) None of the above
Question 2

Which of the follow are viable first line treatment options?

a) Anticoagulants
b) Hemodilution
c) Laser-induced chorioretinal anastomosis
d) Intravitreal aflibercept injection
e) All of the above are first line treatment options
Question 3

What was the conclusion of the Branch Vein Occlusion Study (BVOS)?

a) Laser photocoagulation is recommended as a prophylactic treatment for neovascularization

b) Laser photocoagulation is not a recommended treatment option for BRVO

c) Laser photocoagulation is recommended for patients with macular edema

d) Laser photocoagulation is only recommended for treating vitreous hemorrhages
Question 4

What was the conclusion of The Standard Care vs Corticosteroid for Retinal Vein Occlusion Study (SCORE)?

a) Corticosteroid injection is a better treatment option for macular edema vs grid laser photocoagulation

b) Grid laser photocoagulation is a better treatment option for macular edema vs corticosteroid

c) Corticosteroid injections were found to be extremely unsafe and banned as a treatment option

d) Corticosteroid injections became the first line of treatment as they were found to be highly efficacious and had a great safety profile
Question 5

What was the conclusion of the Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion (BRAVO) study?

a) Ranibizumab was found to have a good safety profile

b) Ranibizumab was shown to be effective in treating macular edema secondary to BRVO

c) Ranibizumab for 6 months caused rapid and sustained improvement in VA

d) A limitation to this study is the control was against sham injections and not laser photocoagulation

e) All of the above are conclusions of the BRAVO study
Question 6

What was the conclusion of the Intravitreal aflibercept (Eylea) for macular edema following branch retinal vein occlusion (VIBRANT) study?

a) Aflibercept is not an effective treatment for macular edema secondary to BRVO

b) Aflibercept is an effective treatment for macular edema secondary to BRVO

c) Grid laser photocoagulation was found to be superior to aflibercept injections in treating macular edema

d) Grid laser photocoagulation and aflibercept yielded the same promising results
Question 7

What was the conclusion of the Bevacizumab for RVO Long-Term Follow Up (BERVOLT) study?

a) Bevacizumab performed well above ranibizumab for treating macular edema
b) Ranibizumab performed well above bevacizumab for treating macular edema
c) Bevacizumab was found to be ineffective in treating macular edema
d) Bevacizumab was found to be effective in treating macular edema but still performing below laser photocoagulation
e) None of the above are conclusions to the BERVOLT study
Question 8

What was the conclusion of Individualized Stabilization Criteria-Driven Ranibizumab versus Laser in Branch Retinal Vein Occlusion (BRIGHTER) study?

a) Ranibizumab monotherapy is superior to laser photocoagulation monotherapy
b) Ranibizumab injections combined with laser photocoagulation produced poor visual outcomes
c) Ranibizumab monotherapy produced the same visual improvement as laser photocoagulation monotherapy
d) Laser photocoagulation monotherapy yielded the best visual outcomes
e) None of the above are conclusions of the BRIGHTER study
Question 9

What was the conclusion of the Ranibizumab Dose Comparison (0.5mg and 2.0mg) and the Role of Laser in the Management of Retinal Vein Occlusion (RELATE) study?

a) Ranibizumab in 0.5mg concentration outperformed 2.0mg concentration

b) Ranibizumab in 2.0mg concentration outperformed 0.5mg concentration, however, more side effects were reported

c) Both concentrations of Ranibizumab, 0.5mg and 2.0mg, yielded the same visual improvement

d) Results are still pending for this study
Question 10

Which new line of treatment has replaced laser photocoagulation as the first line of treatment for BRVO patients?

a) Intravitreal corticosteroid therapy
b) Vitrectomy and arteriovenous decompression
c) Intravitreal anti-VEGF
d) Systemic treatments like carbogen inhalation
e) Nothing, laser photocoagulation is still the first line of treatment