COMPARATIVE CLINICAL AND ECONOMIC EFFECTIVENESS OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS

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Disclosure

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VA Evidence-based Synthesis Program (ESP) Overview

- Sponsored by VA Office of Research and Development and the Quality Enhancement Research Initiative (QUERI)
- Established to provide timely and accurate syntheses/reviews of healthcare topics identified by VA clinicians, managers, and policy-makers, as they work to improve the health and healthcare of Veterans
- Reports conducted by internationally recognized VA clinician methodologists
- Builds on staff and expertise already in place at the Evidence-based Practice Centers (EPC) designated by AHRQ. Four of these EPCs are also ESP Centers, as shown on the following map.
ESP Center Locations

Coordinating Center
Portland, OR

ESP Center
Portland, OR

ESP Center
Los Angeles, CA

ESP Center
Minneapolis, MN

HSR&D/QUERI,
VACO
Washington, DC

ESP Center
Durham, NC

Evidence-based Synthesis Program (ESP)

VETERANS HEALTH ADMINISTRATION
VA Evidence-based Synthesis Program (ESP) Overview

• Provides evidence syntheses on important clinical practice topics relevant to Veterans. These reports help:
  • develop clinical policies informed by evidence
  • the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures
  • guide the direction of future research to address gaps in clinical knowledge
• Broad topic nomination process – *eg*, VACO, VISNs, field staff – facilitated by the ESP Coordinating Center (Portland) through an online process:
  
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January 2017

Full-length report available on ESP website:
http://www.hsrdr.research.va.gov/publications/esp/reports.cfm
Poll #1:

What is your primary role? (Choose one of the following)

• VA clinician
• VA researcher
• VA administrator, manager or policy-maker
• Non-VA clinician
• Other
Poll #2:

For those who do use these anti-VEGF agents, which one do you use most often? (Choose one of the following)

• Aflibercept (Eylea®)
• Bevacizumab (Avastin®)
• Ranibizumab (Lucentis®)
• I use all three equally
• NA/I do not use these drugs
Anti-VEGF Agents in Ophthalmology

Glenn C. Cockerham, MD
National Program Director
VHA Ophthalmology
VA Palo Alto, CA
Avastin™ (bevacizumab)
Genentech/Roche

- FDA approval in 2004 for adenocarcinoma
- Full-length, murine-derived monoclonal IgG1 Ab
- 2 VEGF binding sites
- Theoretically not a good choice for intraocular use, but good results in 2005 in AMD
- Used off label worldwide for intravitreal injections, including VA
Lucentis™ (ranibizumab)
Roche/Novartis

• FDA approval in 2006 for age-related macular degeneration, later approved for macular edema, diabetic retinopathy, and myopic choroidal neovascularization

• Bevacizumab (148 kDa) was cleaved into smaller fragment (48 kDa), affinity enhanced

• NIH funded a head-to-head study of Lucentis vs Avastin in 2011 (CATT)
Eylea™ (afiblercept)  
Regeneron

- FDA approval in 2011 for age-related macular edema; later approved for diabetic macular edema and diabetic retinopathy
Indications for Anti-VEGF Agents in Ophthalmology

- Conditions that cause blindness due to growth of new blood vessels (neovascularization), bleeding, leakage of fluid (edema) and lipids (exudates)
  - Age-related macular degeneration (AMD)
  - Diabetic retinopathy
  - Retinal vein occlusion
Age-related Macular Degeneration (AMD)

- Most common cause of blindness in adults over 65 years of age
- 10% of patients have neovascular (wet) AMD
- 200,000 new patients in U.S. yearly
Diabetic Retinopathy

- Most common cause of blindness between ages 20 and 65 years
- Diabetic macular edema
- Proliferative diabetic retinopathy
  - Vitreous hemorrhage
  - Retinal detachments
Route of Administration

- Intravitreal route (into the vitreous cavity)
- Topical anesthesia
- Estimated 5 million injections in 2015
Topic Development

- Topic nominated by Dr. Glenn Cockerham
- Scope and Key Questions developed with help from Technical Experts:
  - Ophthalmologists
  - Retina Specialist
  - Clinical Pharmacy Specialist
Key Questions

• **Key Question 1:** What is the comparative *clinical effectiveness* of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?

• **Key Question 2:** What are the comparative *harms* of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?

• **Key Question 3:** What is the comparative *cost-effectiveness* of anti-VEGF agents for retinal/choroidal neovascularization and/or macular edema in adults?
Methods: Data Sources

- Search Strategy:
  - Ovid MEDLINE to December 11, 2015
  - PubMed, Elsevier EMBASE, and Ovid EBM to February 2, 2016

- Grey literature sources: trial registries (e.g., ClinicalTrials.gov)

- Requested Scientific Information Packets for unpublished data from manufacturers
Methods: Study Selection

• Population:
  • Diabetic macular edema (DME)
  • Branch or central retinal vein occlusion (BRVO or CRVO)
  • Neovascular age-related macular degeneration (AMD)
  • Vitreous hemorrhage/proliferative diabetic retinopathy/neovascular glaucoma

• Study Designs: only included head-to-head trials
  • Effectiveness and harms: only controlled clinical trials
  • Cost: SRs, cohort studies, validated modeling studies in the US only
Effectiveness Outcomes

- **Visual acuity:**
  - Mean change: clinically meaningful difference between groups ≥5 letters
  - % gaining 15 or more letters
    - BCVA: best-corrected visual acuity
    - ETDRS letters: Early Treatment of Diabetic Retinopathy Study chart letters

- **Functional status or quality of life**

- **Intermediate outcomes:** e.g., change in central macular/subfield thickness, resolution of subretinal/intraretinal fluid (using OCT)
Methods: Study Selection

Outcomes

• Harms:
  • Ocular: e.g., endophthalmitis, retinal detachment, glaucoma
  • Systemic: e.g., arterial thrombotic events, GI disorders

• Costs:
  • Cost of drug alone; cost of overall treatment
  • # of injections
  • % needing rescue/co-interventions
Methods

- Quality Assessment: Cochrane Risk of Bias Tool (low, unclear, or high risk of bias)
- Performed meta-analyses when appropriate
- Rating the Body of Evidence: consider consistency, precision, study quality, directness
  - High: Very confident that the estimate of effect lies close to the true effect for the outcome
  - Moderate: Moderately confident; findings are likely to be stable
  - Low: Limited confidence; additional evidence needed before concluding that the findings are stable
  - Insufficient: No evidence or no confidence in the estimate of effect
Search results: 3650
- Databases: 6350
- Pearled: 20

Excluded = 6223 references

Pulled for full-text review: 127 references

Excluded = 111 references
- Ineligible study design (eg, not directly comparing anti-VEGF agents): 58
- Systematic reviews or meta-analyses (pearled for eligible trials): 34
- Duplicate papers (eg, additional publications on an included trial): 12
- Ineligible population: 7

Included studies: 16
- AMD: 11
- DME: 3
- BRVO/CRVO: 2

- Wide range in size (arms with 8 to 323 patients)
- Variety of treatment schedules
Patients with AMD: most studied condition (11 trials)
  - Majority of studies:
    - Pro re nata (PRN, “as needed”) treatment schedules alone or in addition to monthly injections
    - Age in late 70s, baseline 55 to 62 ETDRS letters (moderate vision loss)
    - Most achieved mean BCVA ~65 to 70 letters

Bevacizumab vs Ranibizumab:
  - Visual Acuity: no significant difference
  - Quality of Life: only reported by IVAN trial, no difference found
Consistent, high-strength evidence of no difference in mean BCVA improvement

**12 months**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mean difference (95% CI) in ETDRS letters changed: Bevacizumab vs Ranibizumab</th>
<th>Bevacizumab arm: N, mean change (SD)</th>
<th>Ranibizumab arm: N, mean change (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAMD</td>
<td>-1.31 (-4.74 to 2.12)</td>
<td>166, 5.1 (14.1)</td>
<td>166, 6.4 (12.2)</td>
</tr>
<tr>
<td>Biswas 2011</td>
<td>-2.70 (-9.91 to 4.51)</td>
<td>60, 0.5 (17.2)</td>
<td>60, 3.2 (12.9)</td>
</tr>
<tr>
<td>CATTa</td>
<td>-0.50 (-3.90 to 2.90)</td>
<td>286, 8.0 (16.9)</td>
<td>301, 8.5 (13.9)</td>
</tr>
<tr>
<td>GEFAL</td>
<td>2.36 (-0.72 to 5.44)</td>
<td>255, 4.8 (14.9)</td>
<td>246, 2.9 (15.1)</td>
</tr>
<tr>
<td>IVAN</td>
<td>-1.66 (-3.82 to 0.50)</td>
<td>305, 4.7 (12.3)</td>
<td>323, 6.4 (12.5)</td>
</tr>
<tr>
<td>LUCAS</td>
<td>-0.20 (-2.55 to 2.15)</td>
<td>220, 7.8 (15.7)</td>
<td>221, 8.0 (14.2)</td>
</tr>
<tr>
<td>MANTA</td>
<td>0.80 (-4.81 to 6.41)</td>
<td>154, 4.9 (13.2)</td>
<td>163, 4.1 (13.4)</td>
</tr>
<tr>
<td>Scholler 2014</td>
<td>6.75 (-1.19 to 14.69)</td>
<td>26, 7.3 (15.3)</td>
<td>29, 0.6 (14.6)</td>
</tr>
<tr>
<td>Subramanian 2010</td>
<td>1.30 (-6.38 to 8.98)</td>
<td>20, 7.6 (15.1)</td>
<td>8, 6.3 (15.5)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>-0.22 (-1.43 to 1.00)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Similar results at 18 to 24 months (4 trials)

*BCVA = best corrected visual acuity*
Moderate-strength evidence of no difference in % gaining ≥15 letters

12 months

<table>
<thead>
<tr>
<th>Trial</th>
<th>RR (95% CI)</th>
<th>Patients gaining ≥ 15 ETDRS letters, n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>BRAMD</td>
<td>1.22 (0.80 to 1.85)</td>
<td>39/166</td>
</tr>
<tr>
<td>CATT(^a)</td>
<td>0.90 (0.71 to 1.15)</td>
<td>83/286</td>
</tr>
<tr>
<td>GEFAL</td>
<td>0.96 (0.64 to 1.45)</td>
<td>39/255</td>
</tr>
<tr>
<td>IVAN</td>
<td>0.66 (0.46 to 0.95)</td>
<td>40/305</td>
</tr>
<tr>
<td>LUCAS</td>
<td>0.94 (0.66 to 1.34)</td>
<td>47/220</td>
</tr>
<tr>
<td>MANTA</td>
<td>1.09 (0.72 to 1.64)</td>
<td>36/154</td>
</tr>
<tr>
<td>Subramanian 2010</td>
<td>2.00 (0.27 to 14.55)</td>
<td>5/20</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>0.93 (0.80 to 1.07)</strong></td>
<td><strong>289/1406</strong></td>
</tr>
</tbody>
</table>

\(^a\)Subramanian 2010

- Favors ranibizumab  Favors bevacizumab

- Similar results at 18 to 24 months (4 trials)
KQ 1: Comparative Effectiveness for AMD

**Afliibercept vs Ranibizumab:**
- 2 large sister trials: VIEW 1 and VIEW 2 (~1230 patients per trial)
- Mean change in BCVA: conflicting results, but no clinically meaningful difference at 12 or 22 months (insufficient evidence)
- % gaining ≥15 letters: no significant difference (low-strength evidence)
- No significant differences in visual acuity between *bimonthly* aflibercept and *monthly* ranibizumab (no bimonthly ranibizumab arm)

**Afliibercept vs Bevacizumab:** no evidence
KQ 1: Comparative Effectiveness for DME

- Patients with DME: 3 trials
  - Largest trial: DRCR.net Protocol T, compared all 3 agents

**Bevacizumab vs Ranibizumab:**
- Visual Acuity: no significant difference (moderate-strength evidence)
Moderate-strength evidence of no difference in mean BCVA improvement at 12 months

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mean difference (95% CI) Bevacizumab arm: N, mean change (SD)</th>
<th>Bevacizumab arm: N, mean change (SD)</th>
<th>Ranibizumab arm: N, mean change (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRCR</td>
<td>-1.40 (-3.20 to 0.40)</td>
<td>218, 9.7 (10.1)</td>
<td>218, 11.2 (9.4)</td>
</tr>
<tr>
<td>Eckinci 2014</td>
<td>2.00 (-4.47 to 8.47)</td>
<td>50, 12.0 (16.6)</td>
<td>50, 10.0 (16.4)</td>
</tr>
<tr>
<td>Nepomuceno 2013</td>
<td>-2.00 (-10.47 to 6.47)</td>
<td>34, 11.0 (17.3)</td>
<td>29, 13.0 (17.0)</td>
</tr>
<tr>
<td>Overall</td>
<td>-1.19 (-2.89 to 0.51)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( \hat{I} = 0.0\%, P = .600 \)

*BCVA = best corrected visual acuity
Moderate-strength evidence of no difference
in % gaining ≥15 letters at 12 months

<table>
<thead>
<tr>
<th>Trial</th>
<th>RR (95% CI)</th>
<th>Patients gaining ≥ 15 letters, n/N</th>
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<tbody>
<tr>
<td></td>
<td>Bevacizumab</td>
<td>Ranibizumab</td>
</tr>
<tr>
<td>DRCR</td>
<td>0.89 (0.66 to 1.20)</td>
<td>59/218</td>
</tr>
<tr>
<td>Nepomuceno 2013</td>
<td>0.79 (0.45 to 1.40)</td>
<td>13/34</td>
</tr>
<tr>
<td>Overall</td>
<td>0.87 (0.67 to 1.13)</td>
<td>72/252</td>
</tr>
</tbody>
</table>

(I² = 0.0%, P = .711)
KQ 1: Comparative Effectiveness for DME

Afiblercept vs Bevacizumab: DRCR.net Protocol T

- Visual Acuity: some benefit in favor of aflibercept, but difference was not likely clinically meaningful in overall population (low-strength evidence)
  - In subgroup with lower baseline visual acuity, difference was clinically meaningful at 12 months: 6.5 letters (95% CI, 2.9-10.1)
  - Difference slightly smaller by 24 months: 4.7 letters (95% CI, 0.5-8.8)
KQ 1: Comparative Effectiveness for DME

Aflibercept vs Ranibizumab: DRCR.net Protocol T

- Visual Acuity: some benefit in favor of aflibercept in the short-term, but difference was not likely clinically meaningful (low-strength evidence)
  - In subgroup with lower baseline visual acuity, difference more pronounced but still did not reach clinical significance: 4.7 letters (95% CI, 1.4-8.0)
KQ 1: Comparative Effectiveness for RVO

• Patients with RVO:
  • 2 small trials at 6 months (177 patients total)

Bevacizumab vs Ranibizumab:
• Visual Acuity: no difference (insufficient evidence)
No difference in mean BCVA improvement (insufficient evidence)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mean difference (95% CI) in ETDRS letters changed: Bevacizumab vs Ranibizumab</th>
<th>Bevacizumab arm: N, mean change (SD)</th>
<th>Ranibizumab arm: N, mean change (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MARVEL</td>
<td>-2.50 (-9.00 to 4.00)</td>
<td>38, 15.6 (13.4)</td>
<td>37, 18.1 (15.2)</td>
</tr>
<tr>
<td>CRAVE</td>
<td>0.00 (-6.26 to 6.26)</td>
<td>51, 16.0 (23.0)</td>
<td>51, 16.0 (16.0)</td>
</tr>
<tr>
<td>Overall</td>
<td>-1.20 (-5.71 to 3.31)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

($\hat{\rho} = 0.0\%, \ P = .587$)

← Favors ranibizumab  Favors bevacizumab →
KQ 2: Comparative Harms

- 12 trials reported harms (9 in patients with AMD)
- \( P \)-values not reported in many trials
- No trials specifically designed to assess harms (not powered)

**AMD:**

- Low rate of withdrawals due to adverse events (<1 to 4.5%)
- Serious ocular adverse events: generally low, no significant differences reported between groups (low- to moderate-strength)
  - Endophthalmitis generally occurred in <1% of patients (5 trials), no significant difference between drugs
  - Other serious ocular adverse events very rare (<1% in 5 trials)
KQ 2: Comparative Harms

AMD (continued):

- Systemic adverse events:
  - % with ≥1 serious systemic harms varied widely (10 to 40%)
  - Similar rates reported in most trials
  - CATT had highest rates and was only trial to find significant difference (relative risk [RR] for bevacizumab vs ranibizumab: 1.30)
  - *But meaning is unclear*, since most of the difference was in harms not known to be affected by the VEGF pathway
  - Arterial thrombotic events occurred in up to 5% of patients; one trial found higher rates in ranibizumab vs bevacizumab at 12 months, but no difference by 24 months
KQ 2: Comparative Harms

DME:

- Data primarily from DRCR.net Protocol T
- Serious ocular adverse events: no significant differences between drugs
  - Endophthalmitis: only 1 patient (<0.5% of patients) over 24 months (higher rates in 2 smaller trials)
  - Most common were elevated intraocular pressure (15.3% of patients) and vitreous hemorrhage (6.4% of patients)
- Serious systemic adverse events: high rates
  - Ranibizumab had more arterial thrombotic events than aflibercept ($P=0.047$) or bevacizumab ($P=0.20$) as well as slightly higher rates of hypertension
KQ 2: Comparative Harms

RVO:

• Two small trials provide insufficient data
• Serious ocular adverse events were relatively rare, no instances of endophthalmitis
KQ 3: Comparative Costs

**Cost:** moderate-strength evidence that ranibizumab and aflibercept are considerably more expensive than compounded bevacizumab and provide no incremental cost-effectiveness benefits

- Two trials: both used compounded bevacizumab
  - CATT: ranibizumab vs compounded bevacizumab for AMD
    - Ranibizumab 35+ times more expensive than bevacizumab (drug only)
  - DRCR.net Protocol T: all 3 agents for DME
    - Total mean costs per participant/year: **$26,000 aflibercept vs 18,600 ranibizumab vs 4,100 bevacizumab**
    - Validated model projecting 10-year costs:
      - Lower BCVA at baseline: incremental cost-effectiveness ratios for aflibercept was **$287,000 per QALY vs bevacizumab**
Limitations

- Methodological limitations of included studies
- Limited data on aflibercept, patients with RVO
- Several trials excluded patients with cardiovascular risk factors
- Only one trial stratified by baseline visual acuity
- All evidence on cost used compounded bevacizumab
- Only controlled trials included for effectiveness and harms data
- Examining clinical populations separately limited our power to detect differences
KQ 1: Comparative Effectiveness

• No clear, consistent, clinically meaningful differences between anti-VEGF drugs were found for the general population (low- to moderate-strength evidence for AMD and DME)
  • Insufficient evidence for RVO
• DME trial: Afiblercept may be superior in patients with lower baseline visual acuity over the short-term
  • Longer-term findings are unclear
  • More trials of afiblercept are needed
Summary

KQ 2: Comparative Harms
- Low rates of serious ocular adverse events
- No clear differences in rates of systemic adverse events

KQ 3: Cost Effectiveness
- Compounded bevacizumab is associated with considerably lower costs than other 2 agents; no data on non-compounded costs

Clinicians should also consider patient preference, individual treatment response, convenience, and distance to treatment facility when choosing amongst these anti-VEGF agents.
VA Costs for Anti-VEGF Agents

- Bevacizumab 4 ml vial $503
- Ranibizumab 0.3 mg (DME) $859
- Ranibizumab 0.5 mg (AMD, RVO) $1437
- Afiblercept 2 mg $1412

- Courtesy of Dr. Debbie Khachikian, Pharmacy Benefits Manager
<table>
<thead>
<tr>
<th>Product Description</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept 2 mg, 0.05 ml</td>
<td>$67,730,000</td>
</tr>
<tr>
<td>*Bevacizumab 25 mg/ml, 4 ml</td>
<td>$15,621,000</td>
</tr>
<tr>
<td>Ranibizumab 0.3 mg/0.05 ml</td>
<td>$8,481,000</td>
</tr>
<tr>
<td>Ranibizumab 0.5 mg/0.05 ml</td>
<td>$1,420,000</td>
</tr>
</tbody>
</table>

* Bevacizumab utilized by both Ophthalmology and Oncology
Anti-VEGF Agents in Medicare and VA Costs 2005-2011

- Indication: age-related macular degeneration
- Bevacizumab (Avastin, Genentech/Roche)
  - $50 per dose in Medicare population (multiple doses from vial)
- Ranibizumab (Lucentis, Genentech/Roche)
  - $1000 per dose estimated
- Bevacizumab used more frequently over time in both Medicare and VA
- Incentives in Medicare may influence drug choice:
  - Patient incentive: have lower copays with less expensive drug
  - Physician incentive: higher reimbursement for more expensive drug; CMS pays physician 6% of drug cost as overhead

Potential Cost Savings with Bevacizumab Use

- Medicare savings: $18 billion
- Beneficiary copayment savings: $5 billion
- (Over 10 year period if all patients treated with bevacizumab alone)

Questions?

If you have further questions, please feel free to contact:

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Devan Kansagara, MD, MCR (Portland ESP Director): kansagar@ohsu.edu

Glenn Cockerham, MD (National Program Director, VHA Ophthalmology Service): Glenn.Cockerham@va.gov

Full-length report and cyberseminar available on ESP website: http://www.hsrdr.research.va.gov/publications/esp/