DRCRnet

Randomized Trial of Intravitreous Aflibercept versus Intravitreous Bevacizumab + Deferred Aflibercept for Treatment of Central-Involved DME: Protocol AC

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National Institutes of Health
National Eye Institute

NIH National Institute of Diabetes and Digestive and Kidney Diseases

NIH National Eye Institute

1

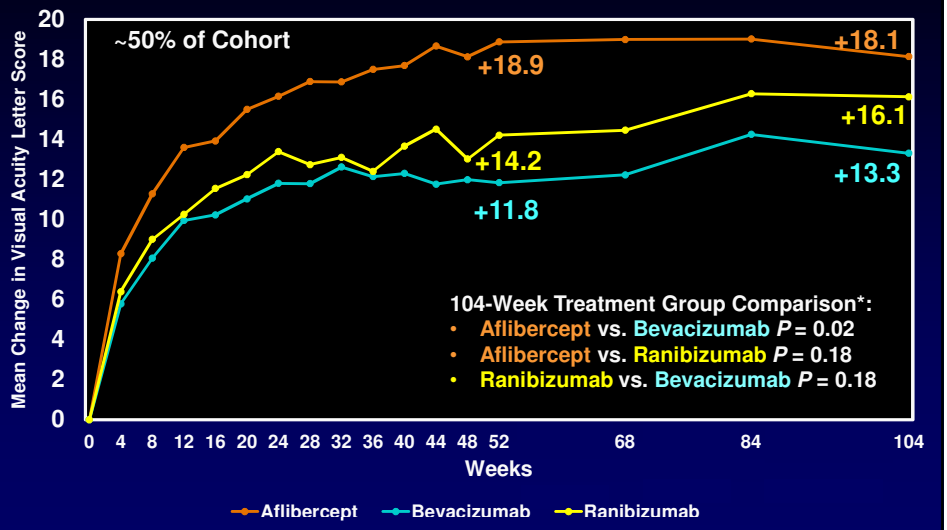
Background

- Aflibercept treatment in Protocol T resulted in better VA, on average, for eyes with worse baseline VA than bevacizumab at 1 year and 2 years, and over 2 years

2

Mean Change in Visual Acuity Over 2 Years

Baseline Visual Acuity 20/50 or Worse



[52-Week: A vs. B $P < 0.001$ / A vs. R $P = 0.003$ / R vs. B $P = 0.21$]

* *P*-values adjusted for baseline visual acuity and multiple comparisons

3

Background

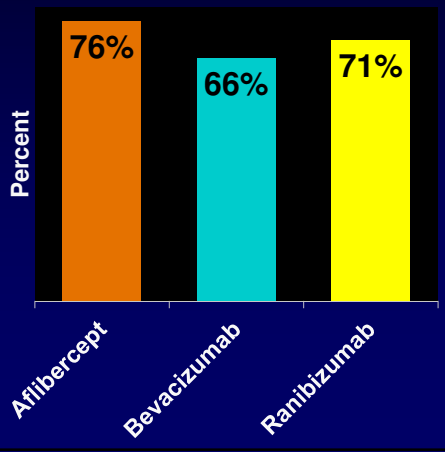
- However, bevacizumab was effective for many eyes with worse VA at baseline.
  - *Approximately 2/3 of bevacizumab-treated eyes had ≥10 letter improvement at 2 years*
  - *Almost half had resolution of DME at 2 years*

4

≥10 Letter Improvement at 2 Years

Baseline Visual Acuity 20/50 or worse

Observed Data



Treatment Group Comparisons*

	Adjusted Difference	CI	*P*-Value
Aflibercept vs Bevacizumab	+10%	-6% to +26%	0.35
Aflibercept vs Ranibizumab	+3%	-9% to +15%	0.57
Ranibizumab vs Bevacizumab	+7%	-6% to +20%	0.57

* *P*-values adjusted for baseline visual acuity and multiple comparisons

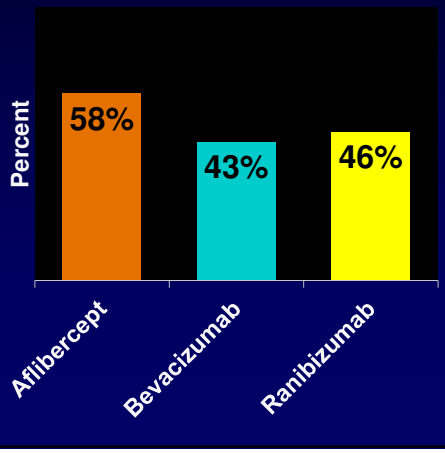
5

≥15 Letter Improvement

Over 2 Years: Mean AUC

Baseline VA20/50 or Worse

Observed Data



Treatment Group Comparisons*

	Adjusted Difference	CI	*P*-Value
Aflibercept vs Bevacizumab	+13%	+1 to +25%	0.02
Aflibercept vs Ranibizumab	+11%	0% to +22	0.05
Ranibizumab vs Bevacizumab	+2%	-7% to +12%	0.64

* *P*-values adjusted for baseline visual acuity and multiple comparisons

6

Background

- **Application in Clinical Practice Settings:**
  - Can we start with bevacizumab, switch to aflibercept and obtain a similar outcome in the long-run compared to aflibercept injections alone?
  - What are the implications of insurance companies mandating this approach or patients choosing this approach?
    - Cost savings
    - Visual outcomes

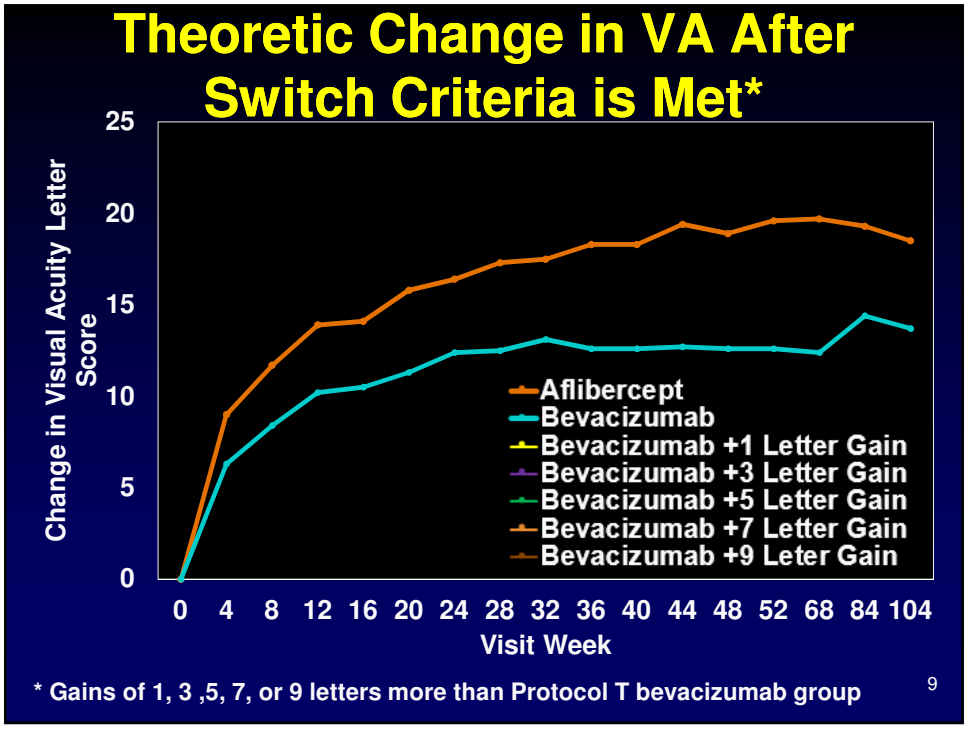
7

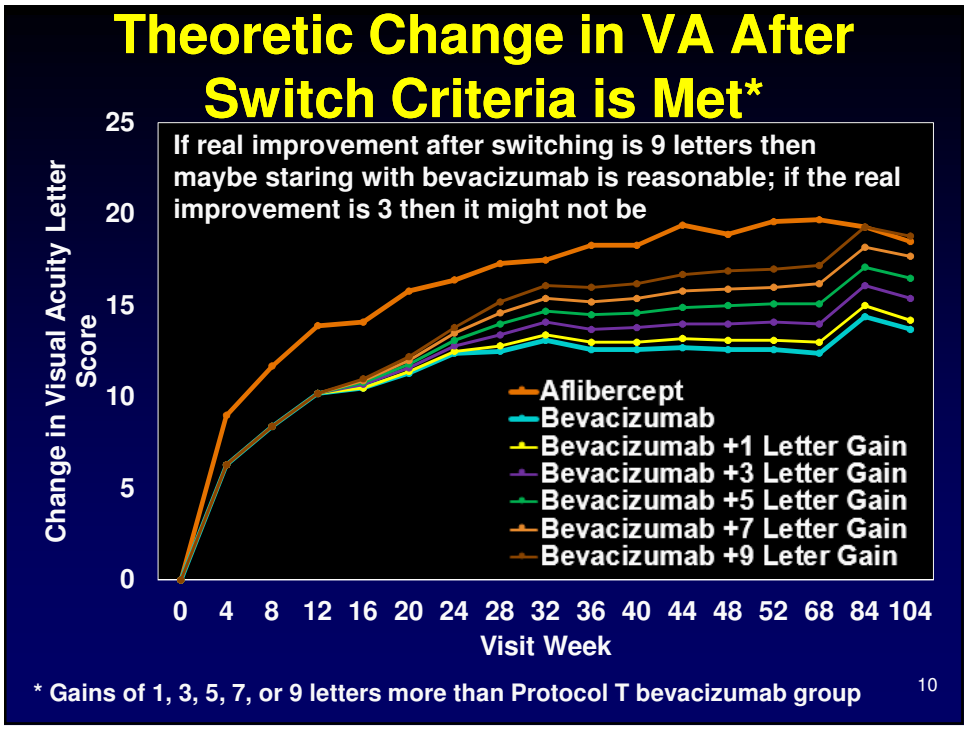
Background

- Based on Protocol T data, it is unknown whether starting with bevacizumab and switching to aflibercept may result in outcomes that catch-up to results if initially start with aflibercept

- Whether or not the switch group catches up will depend on the effect of aflibercept after the switch

8


Theoretic Change in VA After Switch Criteria is Met*
Change in Visual Acuity Letter Score
25
20
15
10
5
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 68 84 104
Visit Week
Aflibercept
Bevacizumab
Bevacizumab +1 Letter Gain
Bevacizumab +3 Letter Gain
Bevacizumab +5 Letter Gain
Bevacizumab +7 Letter Gain
Bevacizumab +9 Leter Gain
* Gains of 1, 3 ,5, 7, or 9 letters more than Protocol T bevacizumab group
9


Theoretic Change in VA After Switch Criteria is Met*
If real improvement after switching is 9 letters then maybe staring with bevacizumab is reasonable; if the real improvement is 3 then it might not be
Change in Visual Acuity Letter Score
25
20
15
10
5
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 68 84 104
Visit Week
Aflibercept
Bevacizumab
Bevacizumab +1 Letter Gain
Bevacizumab +3 Letter Gain
Bevacizumab +5 Letter Gain
Bevacizumab +7 Letter Gain
Bevacizumab +9 Leter Gain
* Gains of 1, 3, 5, 7, or 9 letters more than Protocol T bevacizumab group
10

Study Objective

- To compare the efficacy of intravitreous aflibercept with intravitreous bevacizumab + deferred aflibercept if needed in eyes with center-involved DME and moderate vision loss.

11

Study Design

Multi-Center Randomized Clinical Trial
(312 Eyes, 260 Participants)

At least 1 eye that meets all of the following criteria:

- VA letter score ≤ 68 and ≥ 24 (≈20/50 to 20/320)
- Ophthalmoscopic evidence of CI-DME
- Central-involved thickening on OCT
  - Cirrus: ≥ 290 µm for women; ≥ 305 µm for men
  - Spectralis: ≥ 305µm for women; ≥ 320 µm for men
- No history of anti-VEGF treatment for DME in past 12 months and no history of any other treatment for DME in past 4 months
- No history of major ocular surgery within prior 4 months or anticipated within next 6 months

Aflibercept → **Bevacizumab (Aflibercept if needed)**

Primary Outcome: Mean change in VA over 2 years (area under the curve)

12

Informed Consent Process

- Given T results, consent process is critical to ensure that participant fully understands treatment options and prior treatment results
- Important to ensure a consistent message is given to participants.
- Informed consent includes:
  - Standard Informed Consent Form process
    - Review ICF with coordinator and investigator
    - Signed by participant and investigator

13

Informed Consent Process

- Informed consent includes (Cont):
  - Short mandatory video explaining the rationale for the study (Eng and Sp versions):
    - Protocol T results
    - Price differences between the aflibercept and bevacizumab under a few different insurance circumstances
  - A few questions for the participant to answer
    - To be used as a tool to ensure participant's understanding of the study
    - Investigator and coordinator to educate participant on any missed questions

14

Randomization

- IMPORTANT - investigator MUST:
  - Confirm eligibility
  - Confirm patient's willingness to accept any of the treatment assignments and to complete all treatment/follow-up
  - Be able to perform injection <u>that day</u>
    - If the participant has two study eyes, it is strongly encouraged to treat both eyes that day.
    - If only one study eye injection will be given on the day of randomization, the second study eye injection must be within 7 days.

15

Follow-up Schedule

*The first two times an injection is deferred, the subject will return in 4 weeks for re-evaluation. If deferral continues, the subject will return in 8 weeks for re-evaluation before beginning the every 16 week schedule.

16

Schedule of Study Procedures

Visit	Baseline	Annual visits (52 and 104 week)	All other study visits
BCVA	X	X	X
Eye Exam	X	X	X
OCT	X	X	X
Fundus Photography[a]	X	X	
Blood Pressure	X	X	
HbA1c	X	X	

a - 7MF, 4WF, or UWF

17

Treatment Groups

Aflibercept

- 2.0-mg intravitreous aflibercept

Bevacizumab (Aflibercept if needed)

- Centrally repackaged 1.25-mg bevacizumab
- Switched to intravitreous aflibercept if eye is not “successful”

18

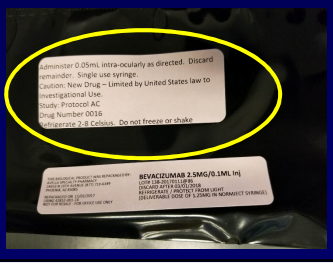
Study Treatment Overview

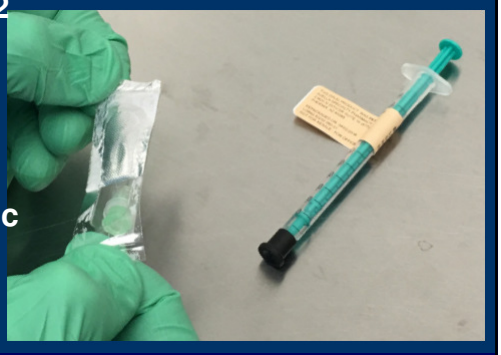
- At randomization, study eyes will receive an intravitreous injection according to their assigned treatment group
- After the initial injection, each eye will be treated according to the retreatment protocol (Protocol T retreatment criteria).
- Bevacizumab will be provided by DRCR.net and will have a study drug number
- Aflibercept will be from your clinic stock

19

Study Bevacizumab

- Bevacizumab will be repackaged by a central pharmacy into Norm-Ject syringes
  - Single-use syringe and 32 gauge needle
  - 0.1 mL fill
  - Drug expires within 3 months of repackaging; keep small supply in clinic





- DRCR drug number label will be on the syringe package only

20

Aflibercept Reimbursement

- Each site will be responsible for acquiring aflibercept for study participant injections
- If needed, reimbursement for aflibercept (drug and injection) will be obtained through:
  - Participant's insurance
  - DRCR.net will reimburse the site for the participant's out-of-pocket expenses up to the cost of aflibercept at the rate Medicare reimburses
    - if an insurance claim is denied
    - if a co-pay is required (invoice DRCR for the co-pay)
    - if a participant does not have insurance
- Please also use assistance programs or samples if possible.

21

Intravitreous Injection Procedure

- ***Two individuals*** must confirm the study eye and drug against the printout or website
- Mark the eye for injection
- Apply topical anesthetic
  - Subconjunctival anesthetic may only be given if topical anesthetic is not sufficient to minimize discomfort
- Retract the eyelids away from the injection site (use of a lid speculum is optional)
- Apply povidone iodine directly over and surrounding the injection site
  - DRCR.net injections must NOT be given without the use of povidone iodine in any circumstance
- Pre- and post-injection topical antibiotics **should NOT be used**

22

Intravitreous Injection Procedure

- ***Masking: The two drugs in this study are packaged and prepared differently***
- Prepare the drug out of view of the participant
  - For example, behind the participant or with your back to the participant so you are blocking their view
- Keep the drug packaging out of the participant's view

23

Early Switching Criteria

- *Concept:* 3-5 bevacizumab injections and eye has not improved and vision is still poor
- *Details:* At the 3, 4, and 5 month visit, study eyes assigned to the bevacizumab (aflibercept if needed) group will switch from bevacizumab injections to aflibercept injections *the first time all of the following criteria are met at 2 consecutive visits:*
  - OCT CST is above the following cutoffs:
    - Cirrus: ≥290µm in women or ≥ 305µm in men
    - Spectralis: ≥ 305µm in women or ≥320µm in men
  - OCT CST has not improved at least 10% from prior visit
  - VA has not improved 5 letters from prior visit
  - VA is 20/50 or worse

24

Additional Switching Criteria

- ***Concept*: At least 6 bevacizumab injections, eye is no longer improving and VA is at least mildly reduced**
- ***Details*: Beginning at the 6 month visit, study eyes that have not already switched to aflibercept will switch *the first time all of the following criteria are met at 2 consecutive visits*:**
  - **OCT CST is above the following cutoffs:**
    - **Cirrus: ≥290µm in women or ≥ 305µm in men**
    - **Spectralis: ≥ 305µm in women or ≥320µm in men**
  - **OCT CST has not improved at least 10% from prior visit**
  - **VA has not improved at least 5 letters from prior visit**
  - **VA is 20/32 or worse**

25

Choosing the Switch Criteria

- **During protocol development, statistical analyses were performed applying various switching criteria to the Protocol T data**
- **Under the proposed criteria, we expect about 50% of the bevacizumab group to meet the criteria to switch to aflibercept injections**

26

The Switch

- Eyes assigned to the bevacizumab group that meet the switch criteria will receive 2 initial monthly injections of aflibercept, then will continue with aflibercept injections throughout study according to the T retreatment regimen

27

The Switch

- If bevacizumab injections are deferred because of success according to the initial retreatment protocol and then the eye worsens, injections will resume using bevacizumab.
- Then the eye will be switched to aflibercept using the same criteria listed previously, following two consecutive bevacizumab injections.

28

Failure Criteria

- For study eyes in both treatment groups, when failure criteria is met, treatment is up to investigator discretion
- Treatment with focal/grid laser will not be permitted in the study eye(s) during the study. If the failure criteria is met, treatment (including laser) is up to investigator discretion.

29

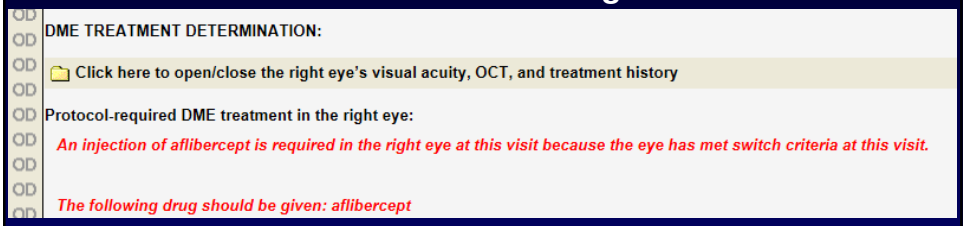
DRCR.net Website

- Like all DRCR.net trials, the website will help guide you through follow-up, including:
  - Assessing eligibility
  - Assessing primary outcome (reminders when imaging, labs are needed)
  - Criteria to switch to aflibercept (bevacizumab group)
  - Retreatment criteria
  - Visit schedule

30

Treatment Message

- Treatment messages (retreatment and switch calculations) depend on ***correct data entry***.
  - Reminder – 2 individuals (investigator and coordinator) must review the treatment messages



- If at any time, you do not believe the message is correct, **contact the CC!**
- If at any time, you wish to deviate from the treatment message, **contact the protocol chair!**

31

Thank You

32