MODULE 10.12
Clinical Studies and Treatment Data - DRCR.net: Protocol T

DRCR.net: Protocol T[1]

Study Name	Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema (DME)
Purpose of study	To compare the safety and efficacy of intravitreous aflibercept, bevacizumab, and ranibizumab in treating DME
Study authors	The Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al.
Published in	*N Engl J Med.* 2015;372:1193-1203.
Study also known as	Protocol T
Subsequent studies	None

Study Overview

A total of 660 participants from 89 clinical sites in the US completed the study.[1] Randomization was as follows: 224 participants in the aflibercept 2.0-mg arm, 218 in the bevacizumab 1.25-mg arm, and 218 in the ranibizumab 0.3-mg arm. Mean Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at baseline was 64.8 (roughly a 20/50 Snellen equivalent); inclusion criteria required baseline visual acuity (VA) to be between 20/32 and 20/320. Baseline mean central subfield thickness (CST) was 412 µm. Subjects were ineligible if they had received anti–vascular endothelial growth factor (anti-VEGF) treatment within the previous 12 months. Only 1 eye from each patient could be enrolled; most patients had bilateral disease, and the contralateral eye was treated with the same agent as was used in the study eye.

The primary outcome was the mean change in VA at 1 year; patients were followed for 2 years.

Study drugs were injected every 4 weeks after an initial baseline dose, unless VA was 20/20 or better with a CST less than the eligibility threshold and there was no improvement or worsening in response to the past 2 injections. Protocol T defined “improvement” as a line gain or a decrease in CST of 10% or more. Worsening was defined as a minimum 5-letter loss or an increase in CST of 10% or more. Regardless of visual or anatomical results at week 24, injections were withheld if there was no improvement or if the patient worsened after 2 consecutive visits. Treatment was reinitiated if either visual or anatomical outcomes worsened.

In cases of persistent diabetic macular edema (DME), laser photocoagulation therapy (focal, grid, or both) was initiated after or at the 24-week visit. Treatment for DME other than the assigned anti-VEGF or laser therapy was allowed only if the study eye met “treatment failure” criteria.

At the primary endpoint (1 year), there was no difference among the drugs in improvement in the VA letter score in eyes with a VA of 20/40 or better (mean improvement, 8 for each drug) or the number of injections (median, 9 for each drug) required to achieve this result. However, “the relative effect varied according to initial visual acuity.”[1]

In patients with an initial baseline VA of 20/50 or worse, there was a statistically significant advantage to aflibercept over ranibizumab and bevacizumab in mean letter score improvements (19 letters, 14 letters, and 12 letters, respectively). All groups started to show improvement in VA by 4 weeks; in eyes with 20/50 or worse baseline VA, “the greater efficacy of aflibercept started to become apparent as early as 4 weeks after the initiation of treatment,” the study authors said.[1] The “magnitude of the greater effect of aflibercept lacked clinical applicability” because baseline VA drove the results.[1]

Similarly, retinal thickness decreased more in the aflibercept and ranibizumab groups than in the bevacizumab group. Anatomical outcomes were also dependent on baseline characteristics, with the relative treatment effect on CST dependent on baseline VA. On average, however, CST decreased by 169 µm with aflibercept, 101 µm with bevacizumab, and 147 µm with ranibizumab,1 but “the anatomical benefit

translated into a visual-acuity benefit only in eyes with a baseline visual acuity of 20/50 or worse."[2]

At 1 year, all eyes had undergone a mean of 9 to 10 injections, with 9 in the aflibercept group, and 10 in the bevacizumab and ranibizumab groups (P = .045). Laser photocoagulation was preformed at least once between weeks 24 and 48 in 37% of the aflibercept-treated eyes (n = 76), 56% of the bevacizumab-treated eyes (n = 115), and 46% of the ranibizumab-treated eyes (n = 95).[1]

When initial VA was 20/32 to 20/40, the median number of injections was 9 in each group, with 36% of aflibercept-treated eyes, 47% of bevacizumab-treated eyes, and 43% of ranibizumab-treated eyes receiving photocoagulation therapy. When initial VA was 20/50 or worse, the median number of injections was 10 in the aflibercept and ranibizumab groups and 11 in the bevacizumab group, with 37%, 50%, and 65%, respectively, of treated eyes receiving photocoagulation therapy.

According to the study authors, "there were no significant differences among the study groups in the rates of serious adverse events (P = .40), hospitalization (P = .51), death (P = .72), or major cardiovascular events (P = .56)."[1]

Study Implications

Martin and Maguire noted 75% of patients with DME present with a baseline VA of 20/40 or better.[2] This study found no significant differences among the 3 drugs when baseline VA was 20/40 or better, meaning cost is likely to be a consideration when planning first-line therapies. The two suggested that based on cost and the findings of Protocol T, "bevacizumab should be considered as first-line therapy in patients with a visual acuity of 20/40 or better."[2]

However, the study authors themselves are quick to note that eligibility criteria for the study "may not apply to eyes with persistent or recurrent diabetic macular edema that are already being treated with anti-VEGF agents."[1]

A post-hoc analysis found more cardiovascular events in patients treated with ranibizumab (37 patients, 17%) than either aflibercept (20 patients, 9%) or bevacizumab (19 patients, 9%); the difference was statistically significant (P = .01). However, these results are anomalistic to other studies on the drugs for DME or age-related macular degeneration, suggesting the differences are a result of chance. However, they do warrant continued surveillance.

The study was funded by the National Institutes of Health, which has a vested monetary interest in the outcomes - bevacizumab is by far the least expensive drug (about $50/injection) but remains off-label. Ranibizumab and aflibercept are more expensive ($1200/dose and $1950/dose, respectively), and in this study each of the 3 was dosed monthly. Aflibercept is approved for every-8-week dosing; ranibizumab is approved for every-4-week dosing. It is unclear if the benefits in patients with 20/50 or worse baseline VA would be similar if aflibercept had been dosed every 8 weeks. The prescribing information for aflibercept acknowledges the drug may be administered every 4 weeks, but that there was no clinical benefit to doing so.[3]

Martin and Maguire recommend aflibercept as the first-line treatment in patients with 20/50 or worse VA, then bevacizumab (because there were no statistical differences between bevacizumab and ranibizumab but there are significant price differences).[2]

However, in a clinical setting, practices sometimes face delays in access to compounded bevacizumab and/or are compensated at a higher rate for using the other anti-VEGFs. Therefore, it is still somewhat unclear which of the 3 anti-VEGFs will be the best option for patients with DME. Protocol T seems to suggest aflibercept is a better alternative in eyes with worse baseline VA, but many patients presenting with baseline VA of 20/40 or better, where efficacy among the 3 was not clinically meaningful. The study is visualized in the inforgraphic the end of this module.

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Take-Home Points

- Aflibercept, bevacizumab, and ranibizumab are effective and relatively safe treatments for DME.
- Bevacizumab is the least expensive drug ($50/injection, off-label). Ranibizumab and aflibercept are more expensive ($1200/dose and $1950/dose, respectively).
- When baseline VA is 20/40 or better, there is little difference between the drugs.
- When baseline VA is 20/50 or worse, aflibercept is more effective at improving vision.

References

1. The Diabetic Retinopathy Clinical Research Network, Wells JA, Glassman AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular 3dema. *N Engl J Med.* 2015;372:1193-1203.

2. Martin DF, Maguire MG. Treatment choice for diabetic macular edema. *N Engl J Med.* 2015;372:1260-1261.

3. Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceutical, Inc; 2014.

DIABETIC VISION LOSS & ITS TREATMENTS

The Angiogenesis Foundation

Protocol T
August 2012 - October 2014

Study Title

Phase 3

DRCR.net Diabetic Retinopathy Clinical Research Network

UNITED STATES
90 Sites Nation-wide

TRIAL AGENT

Aflibercept (Intravitreal Aflibercept Injection (IAI))

Bevacizumab (Intravitreal Bevacizumab Injection (IBI))

Ranibizumab (Intravitreal Ranibizumab Injection (IRI))

STUDY POPULATION

660 eyes, from 660 patients

INCLUSION CRITERIA

- Central Diabetic Macular Edema involvement
- Best-corrected Visual Acuity (BCVA) 20/32 to 20/320 Snellen Equivalent
- Central Subfield Thickness (CST) as measured by Optical Coherance Tomography (OCT) > 250 µm

TRIAL DESIGN

Single -Blind

- Aflibercept (IAI)
- Sham Injection
- Laser (MLT)
- Sham Laser
- Repeating Regimen

ENDPOINTS (measured at 12 months)

PRIMARY

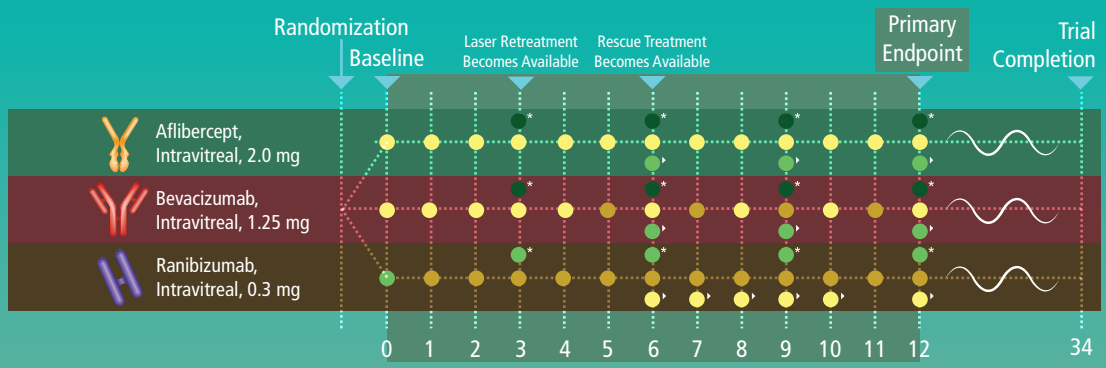
Change in BCVA

SECONDARY

- % of Eyes that gained ≥10 ETDRS Letters
- % of Eyes that gained ≥15 ETDRS Letters
- % of Eyes that gained ≥2-step improvement in ETDRS Diabetic Retinopathy Severity Scale (DRSS) Score
- Change in Central Subfield Thickness (CST), as measured by Optical Coherance Tomography (OCT)
- Change in National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) near activities subscale score
- Change in NEI VFQ-25 distance activities subscale score

*** Laser Retreatment:** Laser or Sham Laser given (as needed) if thickening of the retina or hard exudates present at ≤ 500 µm of macular center, or ≥1 zone of retinal thickening 1 disc area or larger, any part of which within 1 disc diameter of macula center.

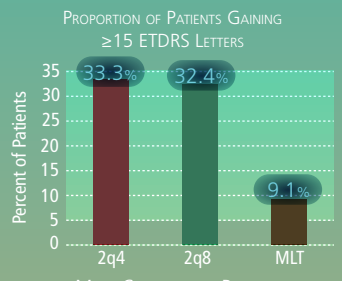
Rescue Treatment: Laser given (as needed) if 2q4 and 2q8 patients lost ≥ 10 letters on 2 consecutive visits or ≥ 15 letters at any 1 visit from the best previous measurement, and BCVA was worse than baseline. For MLT patients, 5 doses of IAI 2mg were given every month, followed by a dose every 2 months.

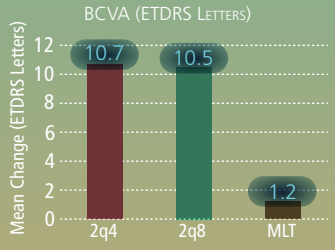


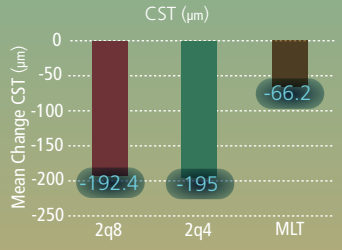
RESULTS

Aflibercept intravitreal injection proved more efficacious in improving vision loss for a greater number of people compared to laser.

- Aflibercept, 2 mg, every 1 month (2q4)
- Aflibercept, 2 mg, every 2 months (2q8)
- Macular Laser Therapy (MLT)





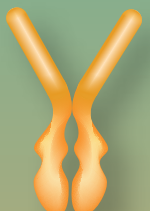


IMPACT

1ST direct comparison between anti-VEGF therapy alone versus laser therapy alone.

- Demonstration of efficacy in non-anti-VEGF naïve eyes
- Based on these results, the FDA approved aflibercept for treatment of DME in July 2014.

SUPERIOR OUTCOMES using



AFLIBERCEPT

* SOURCE - Korobelnik JF, et al. Intravitreal Aflibercept for Diabetic Macular Edema. *Ophthalmology*. 2014 Nov;121(11):2247-54. doi: 10.1016/j.ophtha.2014.05.006. Epub 2014 Jul 8.