CME MONOGRAPH

REVIEW OF RECENT CLINICAL EVIDENCE ADDRESSING TREATMENT STRATEGIES AND OUTCOMES, INCLUDING MANAGEMENT OPTIONS FOR PATIENTS WITH DME

RETINA EDGE

Highlights From Retina Edge Expert Roundtable Discussion

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METHOD OF PARTICIPATION

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HARDWARE/SOFTWARE NEEDED TO PARTICIPATE

High speed internet access

CONTENT SOURCE

This continuing education (CE) activity captures content from a Retina Edge roundtable discussion. Retina Edge gathers leaders in retina to discuss the latest hot topics and cases in retina; the group is led by Dr. Rishi Singh from the Cole Eye Institute Cleveland Clinic.

ACTIVITY DESCRIPTION

Questions remain in clinical practice regarding the optimal selection and use of therapies such as anti-VEGF agents, laser, steroids, and surgical interventions for patients with diabetic macular edema (DME). In addition, because individual patients may respond differently to treatment, guidance is needed regarding when to switch therapies. Through the review of clinical evidence and real-world case studies, this activity will highlight the most appropriate treatment strategies based on disease characteristics and actual treatment outcomes.

TARGET AUDIENCE

This educational activity is intended for retina specialists as well as for comprehensive ophthalmologists and health care providers who are interested in learning about treatment strategies and outcomes for patients with DME.

LEARNING OBJECTIVES

Upon completion of this CE case series, participants will be better able to:

- Highlight recent clinical trial results from Protocol T from the DRCR.net
- Incorporate clinical evidence into DME treatment decisions, with focus on visual and anatomical outcomes, injection frequency, and systemic adverse events
- Recognize when a patient is a nonresponder to an anti-VEGF agent
- Determine when a treatment switch would be beneficial
- Describe current clinical evidence for anti-VEGF therapy for DME with concurrent diabetic retinopathy
- Initiate and select therapies for DME optimally

ACCREDITATION DESIGNATION STATEMENT

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Faculty:

Dr Rishi P. Singh is a consultant/advisory board member for Alcon, Bayer, Bausch & Lomb, Genentech, and Regeneron Pharmaceuticals; Investigator for Alcon, Genentech and Regeneron Pharmaceuticals.

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GRANTOR STATEMENT

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INTRODUCTION

Retina Edge gathered retinal experts together for a roundtable discussion to review the trial design and outcomes of the Diabetic Retinopathy Clinical Research Network (DRCR.net) clinical study Protocol T, a comparative effectiveness and safety study of aflibercept, bevacizumab, and ranibizumab in the treatment of diabetic macular edema (DME). The discussion focused on the implications of Protocol T study results for clinical practice and on what questions remain. The discussion concluded with the analysis of patient cases from faculty files.

PROTOCOL T STUDY DESIGN AND FINDINGS

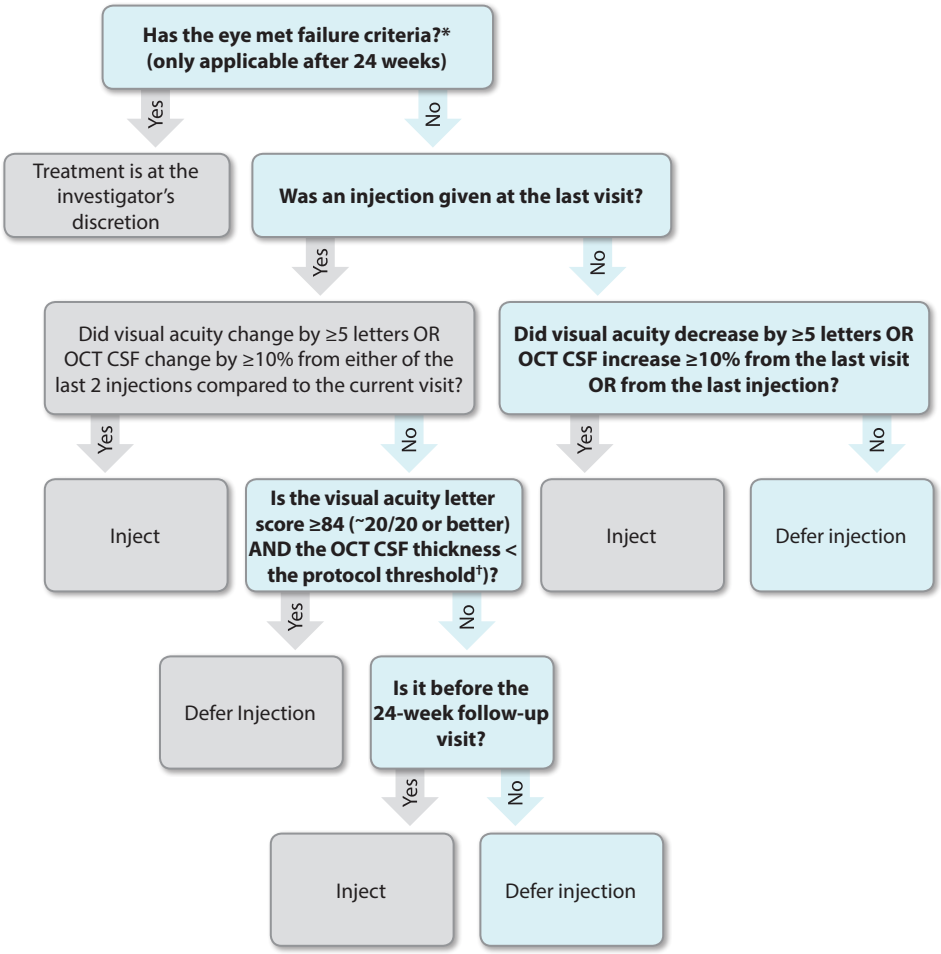
Protocol T was a multicenter, randomized clinical trial comparing the efficacy and safety of aflibercept 2.0 mg, bevacizumab 1.25 mg, and ranibizumab 0.3 mg in patients with type 1 or type 2 diabetes and with at least 1 eye with center-involved DME and no anti-vascular endothelial growth factor (anti-VEGF) treatment within 12 months prior to enrollment (N=660).[1] The mean duration of diabetes was 17 years; the mean visual acuity (VA) at baseline was approximately, 20/50 (Table 1). A little more than a third of patients had prior focal/grid laser photocoagulation, and 11% to 14% had prior anti-VEGF therapy for DME. Treatment was every 4 weeks while the eye was improving or worsening. Treatment was deferred when VA was 20/20 or better, with central subfield thickness (CST) below the eligibility threshold (250 µm to 320 µm) or the eye was stable for 2 injections (Figure 1). The mean improvement in VA letter score was greater with aflibercept than with bevacizumab (13.3 vs 9.7; $P<.001$) or ranibizumab (13.3 vs 11.2; $P=.03$). The relative effect varied according to initial VA, with the mean improvement from baseline increasing with worse initial VA letter score (<69; 20/50 or worse at baseline). In this subpopulation (49% of cohort), mean improvement was +18.9 for aflibercept, +11.8 for bevacizumab, and +14.2 for ranibizumab. The median number of injections (maximum possible 13) was 9 for aflibercept, 10 for bevacizumab, and 10 for ranibizumab. Laser photocoagulation, at least once between 24 and 48 weeks, was performed in 36% of aflibercept-treated eyes, 56% of bevacizumab-treated eyes, and 46% of ranibizumab-treated eyes ($P<.001$ for overall comparison). Retinal thickening was decreased to <250 µm in 66% of aflibercept-treated eyes, 36% of bevacizumab-treated eyes, and 58% of ranibizumab-treated eyes. Bevacizumab was statistically significantly less effective for improving CST outcomes than either aflibercept or ranibizumab.

Table 1. Protocol T Baseline Characteristics and Outcomes at 1 Year [1]

	Aflibercept 2.0 mg (n=224)	Bevacizumab 1.25 mg (n=218)	Ranibizumab 0.3 mg (n=218)
Baseline characteristics			
Median (IQR) duration of diabetes, y	15 (8, 21)	17 (11, 24)	16 (11, 23)
Median (IQR) hemoglobin A1c, %	7.6 (6.8, 9.1)	7.7 (6.8, 8.8)	7.8 (6.9, 9.2)
Prior anti-VEGF for DME, %	11	14	13
Prior focal/grid laser photocoagulation for DME, %	36	39	37
Median (IQR) letter score	69 (74, 59)	69 (72, 60)	68 (73, 58)
Median Snellen equivalent (approximate)	20/40	20/40	20/50
Mean Snellen equivalent (approximate)	20/50	20/50	20/50
20/50 or worse (letter score <69), %	50	49	50
Mean (SD) CST, µm	412 (133)	414 (136)	407 (122)
Outcomes at 1 year	**(n=208)**	**(n=206)**	**(n=206)**
Median (IQR) anti-VEGF injections	9 (8, 11)	10 (8, 12)	10 (8, 11)
Total focal/grid laser treatments between 24 weeks and 1 year, %			
0	63	44	54
1	27	41	37
2	9	15	9
Mean (SD) change from baseline in VA letter score			
Overall	+13.3 (11.1)	+9.7 (10.1)	+11.2 (9.4)
Baseline 20/50 or worse	+18.9 (11.5)	+11.8 (12.0)	+14.2 (10.6)
Mean (SD) CST, µm	240 (70)	311 (124)	257 (88)
Mean (SD) change from baseline, µm	−169 (138)	−101 (121)	−147 (134)
CST <250 µm, %	66	36	58

Abbreviations: CST, central subfield thickness; DME, diabetic macular edema; IQR, interquartile range; SD, standard deviation; VEGF, vascular endothelial growth factor.

Figure 1. Protocol T Study Treatment Flowchart.[1]



**Failure after 24 weeks if OCT CST ≥ eligibility threshold, VA ≥10 letters worse than baseline at 2 consecutive visits, DME on clinical exam reason for VA loss, complete focal/grid laser treatment given, no improvement in VA of >5 letters or >10% OCT CST since last 2 injections, no improvement in VA of >5 letters or >10% OCT CST since last laser treatment, AND ≥13 weeks since last laser treatment.*

Abbreviations: CST, central subfield thickness; OCT, optical coherence tomography; VA, visual acuity.

†Protocol threshold = >250 µm on Zeiss Stratus; ≥320 for men or ≥305 for women on Heidelberg Spectralis; ≥305 for men or ≥290 for women on Zeiss Cirrus.

DISCUSSION

Protocol T Study Design and Real-World Treatment

Rishi Singh: Does the study design of Protocol T reflect real-world treatment?

Diana Do: Technically, since Protocol T is a clinical trial, the results are only applicable to a patient population that is similar to the study participants and who follow the study treatment regimen. In addition, having patients come back every 4 weeks for a year can be a daunting task in real-world practice.

Rishi Singh: Because it is a struggle to have patients come in monthly for evaluation and treatment, how does your routine management deviate from the treatment regimen followed in the Protocol T study?

Diana Do: I treat as needed (PRN) with retreatment criteria that may not be as rigid as Protocol T. In the first year of treating a new DME patient, I discuss with that individual that evaluation every 4 weeks is ideal. However, not every patient I have can follow that strict recommendation. Dosing every 8 weeks with aflibercept (based on the VIVID and VISTA study protocols) is an option in some individuals.[2,3]

Jennifer Sun: Protocol T does reflect how we generally treat patients at the Joslin Diabetes Center, which is an academic tertiary referral center for patients with diabetes. We are helped by the fact that our patient population tends to be compliant (ie, good at keeping their appointment visits) and good about systemic control of their diabetes. But I echo Diana's concerns that, for many people, it is difficult to keep the strict visit windows followed in the clinical trials. At the same time, I think that to obtain the excellent results that we have seen in Protocol T, Protocol I, and other clinical trials, we need to do our best to follow the visit schedules and treatment algorithms that have been used in these studies.

The DRCR.net studies (ie, Protocol I and Protocol T)[1,4] used treatment algorithms to automatically generate treatment decisions via Web-based, real-time data entry and feedback. To do this on a day-to-day basis would otherwise take a huge amount of effort. I think it would be very helpful in clinical practice to have Web-based automated tools to help track VA and OCT [optical coherence tomography] data.

Rishi Singh: Is there a plan to release the tools used in the DRCR.net studies to the general public?

Jennifer Sun: As far as I'm aware, there is no plan at the moment for the Network to disseminate automated or Web-based tools. The network is focused on trying to disseminate the philosophies of the treatment algorithms in a way that helps clinicians transfer these algorithms into clinical practice. In general, we continue to treat eyes with DME that are either improving or worsening from the last visit and we hold treatment in eyes after they have been stable in vision and OCT over 2 injection visits.

Rahul Khurana: I try to emulate Protocol T in clinical practice, although it is quite challenging. Aside from the difficulties just described, there are elements from Protocol T that I find are very helpful. In this study, patients received a minimum of 4 treatments, and if they were not 20/20 and perfectly dry, they received 2 more—essentially a loading dose of

Having patients come back every 4 weeks for a year can be a daunting task in real-world practice.

6 treatments.[1] In general, practitioners are not giving anti-VEGF agents enough time.

When you look at the VIVID and VISTA studies, patients would receive 5 treatments initially.[2] If you look at the RISE and RIDE curves, you see a large benefit after the first 3 injections; however, VA and the retinal anatomy continue to improve for 6 or more injections.[5,6]

Sometimes in practice when you have not gotten a good response after 3 injections, there's a feeling that the treatment is failing. But one aspect of Protocol T that I incorporate in my practice is the 6-treatment loading dose: I allow for 6 treatments before considering changing course or concluding that the anti-VEGF treatment has failed.

Rishi Singh: In Protocol T, the patient would be reinjected if VA was not stable at 20/20. Is that something you do in clinical practice?

Diana Do: I treat based on a combination of symptoms, vision, and OCT findings. Now that we have had many years of experience with intravitreal injections, retinal specialists are very comfortable treating eyes with excellent vision if there is still pathology because we know that these anti-VEGF injections are very safe.

Jennifer Sun: I use both vision and OCT in my decisions to reinject. Even though it is nice to have the quantitative measure of OCT thickness, we know that there is only a moderate correlation between OCT and vision. Our ultimate goal is to maximize our patients' visual function because that is what is going to make a difference in their daily life. I try to inject until the patient's visual potential has been maximized. In Protocol T, we injected until an eye had been stable for 2 or more visits.

Rahul Khurana: One of the practical things that I often do is write down a patient's initial VA on the follow-up notes. That way, when you are in month 5 or 6 of anti-VEGF injections and the OCT and VA are not changing, you can look back at where the VA was initially and realize that letters have been gained. One of the challenges with Protocol T is that it allows you to pause treatment when macular edema is still present. For many retinal specialists when they see macular edema, there is a feeling that the treatment is not working. However, a reminder that the VA has improved is a reminder that the treatment is working—reassurance that you are going in the right direction with the patient's treatment.

FIRST-LINE TREATMENT

Rishi Singh: Is anti-VEGF your first-line treatment? Would any of you consider using laser or a steroid as first-line treatment versus anti-VEGF?

Diana Do: Anti-VEGF agent is my first-line treatment.

Jennifer Sun: I agree, although there are some patients who are unable to comply with monthly visits. For these patients, I would consider using laser as first-line treatment. I potentially might use steroids, although very rarely, because of the side effects associated with steroid use.

Rahul Khurana: There are certain scenarios where I will consider using a dexamethasone intravitreal implant [Ozurdex®, Allergan]. For instance, in a patient who

Recent work from the DRCR.net has shown that anti-VEGF therapy works well in vitrectomized eyes (Protocol I).

is pseudophakic or has difficulty returning for monthly visits. For a patient who is pregnant, the potential systemic effects of anti-VEGF therapy may be a concern and a steroid agent might be a more comfortable choice.

Initially I felt that a steroid implant might be better for the treatment of DME in vitrectomized eyes, based on the CHAMPLAIN study (Table 2)[7]; however, recent work from the DRCR.net has shown that anti-VEGF therapy works well in vitrectomized eyes (Protocol I).[8]

VISUAL ACUITY IN CLINICAL PRACTICE

Rishi Singh: In Protocol T, half of the patients had VA of 20/50 or worse; is this what you see in your clinical practice?

Diana Do: My clinical practice encompasses a large referral pattern and probably slightly more than half of these patients have a visual acuity of 20/50 or worse.

Jennifer Sun: In this era of OCT and increasingly high-resolution imaging, we are catching patients much earlier with DME. As a result, we are seeing a lot of patients with 20/40 and better and even 20/25 or better vision.

RECOGNIZING THERAPY FAILURE

Rishi Singh: How do you define failure of therapy in your practice?

Jennifer Sun: As a referral practice at Joslin, I see a lot of patients who come in to me saying that they have "failed anti-VEGF therapy" elsewhere. I always ask them, "How many injections have you gotten before coming here and what was the frequency of the injections?" Often, they have had only a few injections with long time intervals between treatments, where potentially the effect of the anti-VEGF has worn off and the edema has recurred.

One of the lessons we are seeing increasingly from the clinical trial data and post hoc analyses is that patients who do not necessarily immediately respond after 3 or even 6 injections with complete resolution of thickening or return of vision to 20/20 or better still have a reasonably good chance of responding with subsequent injections. Nonresponse is more likely determined after 9 or 10 injections of anti-VEGF.

Rishi Singh: How do you manage a nonresponder to anti-VEGF therapy?

Jennifer Sun: We discuss with the patient the fact that even if they have had a number of injections before, it is important to perform these injections on a schedule of monthly visits. It is also important to give the anti-VEGF therapy an adequate length of time in terms of the number of treatments to work. I will often restart such patients on anti-VEGF. Sometimes if a patient seems to have had an adequate trial with one anti-VEGF agent, I'll switch within the anti-VEGF class as well.

Diana Do: I agree that the term "treatment failure" is not well defined and used too loosely. I treat DME on an as-needed basis and at the first visit, I tell my patients most eyes with DME will need an average of

Table 2. Dexamethasone Intravitreal Implant for DME in Vitrectomized Eyes[7]

- Study type
  - 6 month, phase 2 study (N = 56)
  - DME, history of pars plana vitrectomy in study eye
- Population
  - Baseline CST ≥275 µm
  - VA between 20/40 and 20/320
  - Mean time since pars plana vitrectomy 31 months
- Mean CST
  - 403.4 µm baseline
  - 247.6 µm week 8
  - 364.5 µm week 26
- Mean decrease in CST from baseline
  - 39% week 8
  - 10% week 26

Source: Boyer DS, et al. *Retina*. 2011;31(5):915-923.

Abbreviations: CST, central subfield thickness; DME, diabetic macular edema; VA, visual acuity.

9 anti-VEGF injections over the first year. I emphasize DME is a chronic condition that needs close follow-up and many anti-VEGF treatments in the initial year of treatment.

Rahul Khurana: It is important how treatment failure is defined. In Protocol T, the mean VA improvement from baseline with aflibercept was 13 letters, which we all think is excellent; however, 34% of the eyes in this group were not dry, so 1 in 3 eyes, despite going through a 9-injection regimen, had persistent fluid.[1] If the patient has VA improvement, some DME may be tolerated. From our experience in AMD [age-related macular degeneration], we want the OCT to be dry, and that is always a good goal, but the anti-VEGF treatment should not be considered having failed based on the lack of dryness alone.

PROTOCOL T EFFICACY OUTCOMES

Rishi Singh: In Protocol T, there were fewer laser treatments in the aflibercept group and 1 less injection, which was not a significant difference (Table 3). Visual acuity was significantly improved, perhaps as a result of the higher molecular dosing used with aflibercept relative to the other agents. What other hypotheses do you have for observed Protocol T results?

Table 3. Protocol T Results[1]	Aflibercept	Bevacizumab	Ranibizumab
Median (IQR) anti-VEGF injections	9 (8, 11)	10 (8, 12)	10 (8, 11)
1 or more focal/grid laser treatments, %	36	56	46

Jennifer Sun: We can hypothesize that some of the difference in results is due to the fact that the binding affinity of aflibercept for VEGF is higher than the other drugs, but we don't fully understand what mechanisms have led to the differences between drugs. The question about dosing is an interesting one, although we have not seen differences in the 0.3 mg and 0.5 mg ranibizumab dosing in the clinical trials RIDE and RISE.[5,6] The results seen in Protocol T were fairly similar to those observed in other studies; we have not seen improved results in other studies with higher doses of ranibizumab.[6] It is also somewhat of a moot point since these are the doses that are commercially available to our patients.

Diana Do: We conducted a mutlicenter, randomized clinical trial (the READ 3 Study) that compared 2.0 mg with 0.5 mg of ranibizumab. The READ 3 results demonstrated that quadrupling the dose did not result in better VA outcomes in DME eyes.[9] This clinical trial demonstrated that we are likely at the top of the dose response curve with ranibizumab. In regards to aflibercept, it is a fusion protein that blocks VEGF and placental growth factor, and inhibiting placental growth factor may provide additional benefit.

Rahul Khurana: The VA gains in Protocol T with all 3 drugs were impressive, which was possibly influenced by the patients included in the study. Protocol T required a 12-month anti-VEGF washout period. In RISE and RIDE, VIVID and VISTA, the washout period was only 3 months.[2] Because many of our patients are already being treated with anti-VEGF, we may not be able to duplicate these impressive results in daily clinical practice.

One of the lessons we are seeing increasingly from the clinical trial data and post hoc analyses is that patients who do not necessarily immediately respond after 3 or even 6 injections with complete resolution of thickening or return of vision to 20/20 or better still have a reasonably good chance of responding with subsequent injections. Nonresponse is more likely determined after 9 or 10 injections of anti-VEGF.

VISUAL ACUITY AND CENTRAL SUBFIELD THICKNESS OUTCOMES

Rishi Singh: Bevacizumab was inferior to both ranibizumab and aflibercept in CST outcomes. Bevacizumab was also inferior to aflibercept in VA outcomes. What are the implications of these findings?

Rahul Khurana: The Protocol T results reaffirm what I see in clinical practice. I always felt that ranibizumab had a better effect than bevacizumab. I was surprised that the differences in VA were not statistically significant. As retinal specialists, we are driven by differences in OCT, so the Protocol T results are consistent with what we see in practice. It is important to note that bevacizumab does work and that the VA results are very similar.

Diana Do: As mentioned earlier, there is only a modest correlation between VA and OCT. So OCT may not be the best single marker to follow for treatment response. It is reassuring that Protocol T showed that all 3 anti-VEGF agents are effective and safe; however, aflibercept had a slight advantage in VA outcomes in eyes that had worse initial vision.

Jennifer Sun: I am really looking forward to the 2-year results from Protocol T. After 1 year, we are seeing a difference in the OCT outcomes. Is there a chance that the bevacizumab-treated eyes will catch up over the course of year 2, or will the CST curves continue to separate? This type of finding could influence our decisions for individual patients.

Rishi Singh: The study concluded that in eyes with VA of 20/50 or worse, aflibercept was favored over the other 2 agents, and that with eyes at 20/40 or better, there was essentially no difference in the VA outcomes (Table 4). Overall, in the whole study, there was a difference of 2 letters favoring aflibercept, although the study deemed this difference to be not clinically meaningful or clinically relevant. How would you apply these findings to clinical practice?

Table 4. Mean Improvement in VA at 1 Year[1]	Aflibercept	Bevacizumab	Ranibizumab
Letter score <69, equivalent to 20/50 or worse, at baseline	+18.9	+11.8	+14.2
Letter score 78-69, equivalent to 20/32 to 20/40, at baseline	+8.0	+7.5	+8.3

Jennifer Sun: Based on the Protocol T results, aflibercept has become my first-line treatment for patients who start out with vision 20/50 and worse. I do keep in mind that electronic ETDRS [Early Treatment Diabetic Retinopathy Study] VA was used in this trial. Patients often do better with that than with typical office charts, but I still use 20/50 as a general threshold.

Use of aflibercept will depend on individual circumstances and payer coverage. For a patient who has no insurance coverage or access to aflibercept, I can reassure them that based on the Protocol T results, they still have an excellent chance of doing well visually with bevacizumab or ranibizumab.

This clinical trial demonstrated that we are likely at the top of the dose response curve with ranibizumab. In regards to aflibercept, it is a fusion protein that blocks VEGF and placental growth factor, an inhibiting placental growth factor may provide additional benefit.

INSURANCE COVERAGE AND MANDATORY STEP THERAPY

Rishi Singh: Are you facing mandatory step therapy in your region from payers?

Jennifer Sun: We have not come across that as a challenge in our region, but I have certainly heard a lot about it from others.

Rishi Singh: Two of our insurance plans in Ohio have instituted step therapy for AMD but not for DME.

Diana Do: I have encountered step therapy in my practice in Nebraska, with insurers recommending strongly we use the bevacizumab first and document no improvement. More recently, there is more difficulty in obtaining bevacizumab because we are required to write the prescription for bevacizumab ahead of time. This slows the speed in which we can examine and treat patients in the same day. This has been a barrier to using bevacizumab. With the Protocol T results, I will use aflibercept more for first-line treatment of DME in eyes with 20/50 vision or worse.

Rahul Khurana: For people who are 20/50 and worse, there is almost a 5-letter difference between aflibercept and ranibizumab, so I will be using aflibercept. It will be interesting to see if results in clinical practice can emulate those obtained in the Protocol T study. Deciding between bevacizumab and the on-label products is always dependent on insurance coverage. Step therapy has slowly started to be implemented in California, especially with small private insurance groups. Because private insurers often won't reimburse for the expensive agents, it is sometimes very difficult to use ranibizumab or aflibercept.

SAFETY CONSIDERATIONS

Rishi Singh: In Protocol T, there were more adverse events of cardiac and vascular disorders in the ranibizumab group. Will this finding affect what you are doing in clinical practice?

Jennifer Sun: The safety discussion always comes right after the efficacy discussion with my patients. Even though we have not seen large increased risks of adverse events with any of the anti-VEGF agents given intravitreally, there are higher rates of thromboembolic events when they are given systemically. I feel I have to mention this whenever we start someone on an anti-VEGF agent for the first time. In general, I tend to say we have not seen major differences in rates of serious adverse events, hospitalizations, or deaths.

Diana Do: Through many years of experience with intravitreal anti-VEGF agents, the totality of data suggests they are very safe. When the questionable increased risk of cardiac adverse events with ranibizumab was noted in Protocol T, it did not really go along with data from previously published studies, so I think it is most likely due to chance. None of our clinical trials are powered to look at a small difference in these very uncommon systemic adverse events. I tell my patients that intravitreal anti-VEGF agents are generally very safe and the chances of having a systemic adverse event are close to nil.

Rahul Khurana: This data has actually reassured me. As you know, diabetic patients are at elevated risk for systemic complications. For instance, patients with DME have a 2-fold higher risk of stroke than diabetic patients without DME. It is reassuring to see that with 1-year data, there was not a higher

In general, I tend to say we have not seen major differences in rates of serious adverse events, hospitalizations, or deaths.

risk of stroke. I feel the cardiovascular anomaly seen in Protocol T was likely by chance; I wouldn't read too much into it.

Rishi Singh: If you have a patient who has recently had a stroke, is there anything you would consider doing differently regarding treatment?

Jennifer Sun: It depends on how recently the stroke occurred. I generally will give the patient a few months to get past that peri-stroke period before starting anti-VEGF, and I might consider starting with a steroid.

Diana Do: I used to debate if I should withhold anti-VEGF therapy in a patient with a recent stroke, but vision is so important to patients' quality of life. I tell patients that there is no evidence to suggest an increased risk of systemic problems with intravitreal VEGF blockers. After an informed consent process, if they are comfortable with the risks and benefits of therapy, I am comfortable using anti-VEGF agents.

Jennifer Sun: One option is to delay treatment, but you do not want someone to go blind on your watch. Fortunately, DME is a very different disease entity from AMD, and we do have the luxury, if we need to, of waiting a few months for someone's systemic status to stabilize without a huge risk of negatively impacting long-term VA outcomes.

Rahul Khurana: I always tell my patients who have had a previous stroke that even if I do nothing, they are at high risk for having another stroke. Previous stroke is one of the largest risk factors for a future stroke. I think it is very important for these patients to be aware of this risk.

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ALTERNATIVE TREATMENT OPTIONS

Rishi Singh: In Protocol T, laser was given at a very low rate. How, if at all, will you incorporate laser in your practice?

Jennifer Sun: I use laser as an adjunct to anti-VEGF therapy. I generally will not start it for the first 6 months of anti-VEGF therapy and I follow the deferred laser guidelines that have been used in the Protocol I DRCR.net trial.[4] I find that in many of my patients, we never need to go to laser. Only about 36% of patients in the aflibercept group in Protocol T received any laser over the first year.

It is nice to have another treatment option such as laser for the patient who has persistent DME past the initial 6 months of anti-VEGF injections. For these patients, I use a PASCAL® laser; for macular treatments, I use the laser on the single-spot setting.

Diana Do: I reserve laser for noncenter-involved DME. I rarely use laser in combination with anti-VEGF therapy for center-involved DME. If I am not getting an optimal response with VEGF inhibitors, then I will switch to a dexamethasone intravitreal implant instead of using laser.

Rahul Khurana: My use of laser has gone down dramatically, and I rarely use laser as a first-line treatment for DME. I might consider it extrafoveally or for a patient who has good VA and does not want to go through the injection regimen.

CASE PRESENTATIONS

CASE 1

A gentleman who has a 10-year history of diabetes presented with bilateral nonproliferative disease: 20/50 in the right eye and 20/40 in the left eye (Figure 2).

Rishi Singh: What would you do?

Diana Do: Given the visual acuity, I would recommend aflibercept. I would offer same-day, bilateral injections if the patient desired.

Jennifer Sun: I agree, especially given the 20/50 vision in his right eye. I would use aflibercept, and I often do bilateral injections. If I am just starting anti-VEGF therapy, I usually start in one eye at the first visit and then, if needed, move to bilateral injections by the second visit. I only do this because patients can be very nervous if they don't know what to expect. I use the first injection as an opportunity to get them comfortable with the procedure. They are usually so much happier at the second visit, because the first injection was a lot less uncomfortable and traumatic than they expected.

Rahul Khurana: I would also treat both eyes with aflibercept. What if there is no macular edema in the right eye and the patient is 20/40 in the left. Does that change your call?

Jennifer Sun: If there were any extenuating circumstances, such as if aflibercept was not covered for this patient, then I would feel very comfortable treating with either ranibizumab or bevacizumab. If aflibercept was covered, then I probably would start with aflibercept, because it might do a little bit better. It might lead to fewer injections and fewer treatments with lasers over time. Additionally, we have more safety data on aflibercept and ranibizumab than we do bevacizumab.

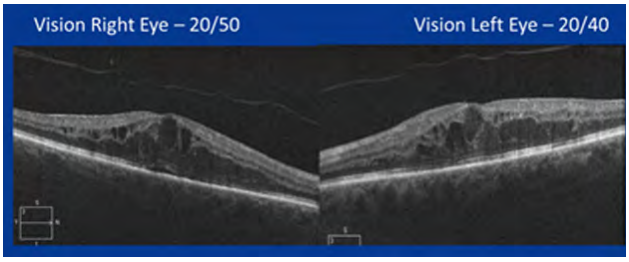
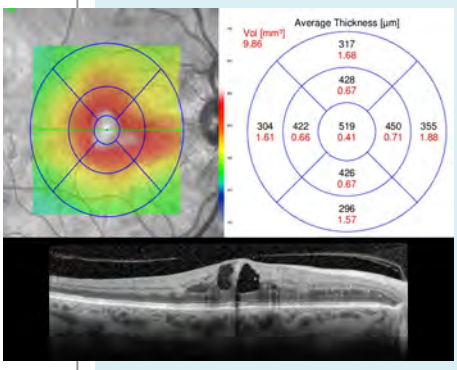


Figure 2. Courtesy of Dr Rishi Singh.

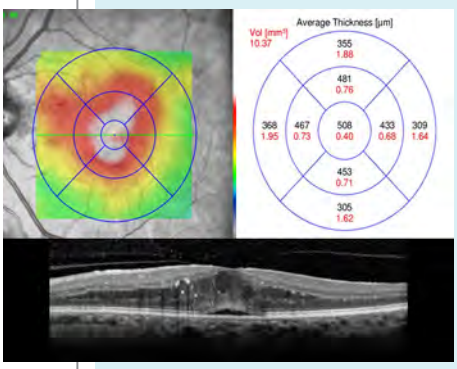
CASE 2

A 58-year-old woman has had type 2 diabetes for 11 years. Her hemoglobin A1C level is 7.5%, and she has no history of prior DME treatment. She came to us after noticing vision loss in her right eye. Upon exam, she had moderate nonproliferative diabetic retinopathy in both eyes, with vision of 20/50 in the right eye and 20/16 in the left eye. Right eye OCT CST was 519 µm; left eye OCT CST was 508 µm (Figure 3).

Figure 3 courtesy of Dr Jennifer Sun.



Right Eye



Left Eye

Jennifer Sun: What first-line treatment would you recommend?

Rahul Khurana: I would treat with aflibercept. Even though the patient's hemoglobin [Hb] A1C of 7.5% indicates acceptable glycemic control, it is reassuring that the effectiveness of anti-VEGF therapy is essentially independent of HbA1C levels.[10] In RISE and RIDE, it was very surprising to see that neither VA nor OCT CST measures were affected by the level of systemic glycemic control.[5] In contrast, in patients who underwent solely laser treatment in the VIVID and VISTA trials, their visual and anatomic outcome were based significantly on their HbA1C value.[11]

Diana Do: I would recommend treatment with aflibercept in the symptomatic right eye, and I would closely observe the asymptomatic left eye. I usually only recommend treatment when the patient feels the vision is blurry. However, this is a striking OCT of the left eye—I am a little surprised that her vision is so good—20/16, but this is another example of how the visual acuity and OCT only have modest correlation.

Jennifer Sun: Since the patient is being treated in the right eye, we would have the luxury of closely following the left eye and regularly doing additional OCT scans. If something changes, we would detect it quickly.

Rahul Khurana: DRCR.net is currently doing a study (Protocol V) that is looking at treating DME with anti-VEGF therapy when vision is good.[12] The conservative approach might be to watch the left eye. If she was my patient, I would watch very closely. The minute the vision drops, I would start treatment. I would feel uncomfortable initiating anti-VEGF treatment in an eye with 20/16 vision unless the results from the DRCR.net Protocol V support treatment.

Jennifer Sun: This patient received 18 injections of aflibercept over 18 months in her right eye. Her final VA was 20/20, 87 letters; OCT CST was 239 µm. The patient responded very well to aflibercept anatomically. Her retina flattened out within the first year of treatment, after approximately 10 or 11 injections. The reason we kept injecting her was because her VA bounced back and forth. She would be 20/25 at one visit and then 20/20 the next and then 20/25 again. I kept treating her because I really wanted to make sure her vision was stable before I took her off the anti-VEGF. She was very compliant and willing to be treated, which allowed us to treat her a little longer than I might have many other patients.

Diana Do: When did you start treating the left eye?

Jennifer Sun: We went with the approach that was mentioned, which was to hold off treating the left eye until we saw a change in the vision. At the very first visit in which her vision dropped by 5 or so letters, we started treatment. She responded well and her vision came back very quickly.

In RISE and RIDE, it was very surprising to see that neither VA nor OCT CST measures were affected by the level of systemic glycemic control.

CASE 3

A 52-year-old woman with moderate cataracts and a history of proliferative diabetic retinopathy presented with blurry vision in both eyes: 20/80 in the right eye and 20/60 in the left eye. Upon exam, she was found to have center-involved DME in both eyes (Figure 4).

Diana Do: In this patient, the FA [fluorescein angiogram] shows the leakage in both eyes (Figure 4A).

Rishi Singh: The patient received 2 bevacizumab injections. What was the time frame in between the injections?

Diana Do: Although a 4-week interval was recommended, the actual time period between injections was 6 weeks because the patient couldn't return sooner. When she did return, there was worse edema in both eyes. We injected bevacizumab again and told her to come back in 4 weeks, which she did, but there was still significant edema (Figure 4B).

Rahul Khurana: It is a little too early to shift direction only 2 treatments in; I usually use a loading dose of 6 injections before I consider changing course. Normally I would say continue with the bevacizumab, but given the recent Protocol T data, I might say switch to aflibercept. I think continuing with an anti-VEGF would be good before switching to something else, such as laser or a steroid.

Jennifer Sun: I agree. I would continue the anti-VEGF. Because this is a phakic patient, I would be reluctant to switch to a steroid, with the thought that the steroid is going to cause cataracts and make her vision worse. Having started with bevacizumab, I would probably just continue the bevacizumab for several more injections, although I agree that now that we have the Protocol T data, I might have started with the aflibercept early on.

Rishi Singh: I think that once treatment has been initiated with bevacizumab, it should continue. I would give at least 4 to 6 injections of bevacizumab before considering a switch.

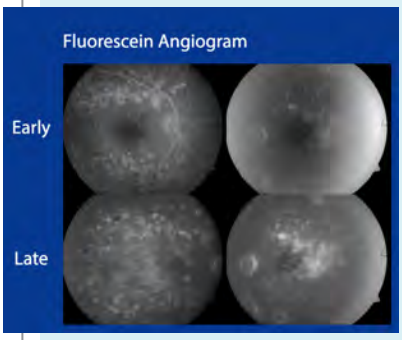
Diana Do: We did recommend switching at the next visit. At the time, we did not have the results of Protocol T yet, so we switched to ranibizumab. There was a better effect initially, but then with subsequent treatment, there was worsening edema.

Rishi Singh: Some people have used the term "tachyphylaxis." Do you think that actually exists? Or do you think this was just the ebb and flow of someone with chronic DME, where the edema can fluctuate?

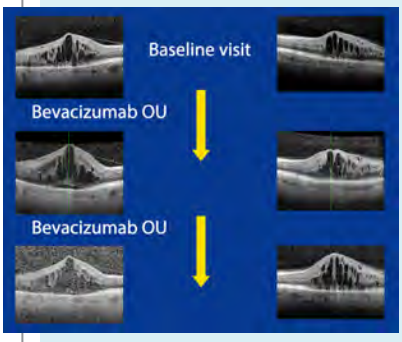
Jennifer Sun: In my patients who get treated with anti-VEGF, if they are coming in monthly, I don't typically see a lot of worsening edema as in this case. I would wonder if something had changed systemically, for example, new kidney failure or kidney issues. I would continue with the same treatment for another month or two just to see, because sometimes you do see these sorts of fluctuations.

Rishi Singh: It may be a challenge, but perhaps bring the patient in 2 weeks after an injection. I have had a patient where doubling the anti-VEGF dose was effective because VEGF load was so high. Some studies have shown wide variations in VEGF levels in aqueous and vitreous samples.[13-15] Whether it really matters clinically in most patients, I don't think so. But in this situation, it may.

Figure 4. Courtesy of Dr Diana Do.



A. Early and late frame angiograms demonstrating diffuse DME with late filling of cystoid spaces.



B. Baseline and follow-up OCTs following 2 treatments with bevacizumab. Note that there was no change in the retinal thickness or contour.

Diana Do: After 2 monthly injections of 0.3 mg ranibizumab, the patient still had significant edema on OCT and was switched to aflibercept. After starting aflibercept, there was more reduction in the DME. I do not have long-term follow-up in this patient yet, so I do not know if this initial beneficial effect with aflibercept will persist or not.

Rahul Khurana: One of the caveats is that in the clinic, if we have a patient who has persistent edema after 3, 6, or 9 shots with anti-VEGF injections, we are likely to switch until we see them dry. It is important to realize that if you just keep treating, it gets better. The hard part to discern is if it is the repeated treating or the switching which is making a difference.

FINAL THOUGHTS ON PROTOCOL T

Jennifer Sun: Protocal T demonstrates that all 3 of these anti-VEGF agents are highly effective for DME. It also shows that you can use a PRN treatment regimen in DME with excellent results. You don't necessarily need monthly continuous injections for years and years; you can taper off anti-VEGF injections and maintain good vision gains.

Diana Do: Protocol T provides retina specialists with more evidence-based medicine. What we have to decide now is how to best use this evidence to take better care of our patients.

Jennifer Sun: The application of the Protocol T results is going to differ from patient to patient, as always, depending on the patients' circumstances, their history, and multiple factors that are outside the realm of what was formally evaluated in Protocol T.

Rahul Khurana: I am most excited that we have 3 highly effective agents to treat DME. It is reassuring to see that they all do work well. The challenge will be applying the protocol in real-world practice.

Rishi Singh: Protocol T has answered many questions, yet key unanswered questions remain. I am interested in understanding whether the findings of Protocol T apply to all patients or if there are additional differences among subgroups yet to be reported. I look forward to seeing the results in greater detail.

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