Announcer Introduction:
Welcome to CME on ReachMD. The following activity, *Diabetic Macular Edema Treatment in the 21st Century*, is brought to you by the DRCR Network, sponsored by the National Eye Institute of the National Institutes of Health, and provided by Prova Education.

Prior to beginning the activity, please review the faculty disclosure statements, as well as the learning objectives.
Your faculty is Dr. Jennifer Sun.

Dr. Sun:
Hello, and welcome to the DRCR Network module on Diabetic Macular Edema Treatment in the 21st Century. By the end of this module, you will understand the DRCR Network (also known as the DRCR.net) treatment algorithm for diabetic macular edema, or DME. You will also recognize the treatment results obtained by using this algorithm. Specific topics that will be covered include: avoiding
under-treatment in the first year of therapy and avoiding over-treatment thereafter, the average number of injections that will be administered over a period of 5 years, safety of deferring injections after 6 months for eyes with persistent, stable DME, and the interaction between initial visual acuity and differences in outcomes among 3 anti-vascular endothelium growth factor, or anti-VEGF agents.

First, some background on the DRCR.net. The Network was established in 2003 through a cooperative agreement with the National Institutes of Health of the United States Department of Health and Human Services. The initial mission of the DRCR.net was to develop and operate a collaborative network to facilitate multicenter clinical research of diabetic retinopathy. This includes proliferative diabetic retinopathy, diabetic macular edema and associated conditions which are leading and growing causes of vision impairment and blindness in the U.S. and throughout the world. As of 2017, the DRCR.net has also expanded its scope to include other non-diabetic retinal diseases such as age-related macular degeneration and retinal vein occlusion.

To date, the DRCR.net has completed and reported primary results for 20 protocols. An additional 7 studies are currently ongoing. These studies have led to 80 publications to date. In this module, we will focus on studies that have led to our current, recommended practice patterns for diabetic macular edema. We will start with results from Protocol I, the first reported phase 3 study of intravitreal ranibizumab or triamcinolone acetonide, in combination with laser photocoagulation for diabetic macular edema.

Before we review the study findings, let's consider this patient whose macular scanning laser ophthalmoscope image shows evidence of lipid and microaneurysms. The corresponding OCT B-scan reveals macular thickening with intraretinal cysts and hyperreflective foci. This patient had decreased vision due to diabetic macular edema. The best corrected visual acuity was 20/63, and central subfield thickness was 462 microns. Let's find out how this common case of DME should typically be treated based on DRCR.net results in the 21st Century.

Based on DRCR.net results first reported in 2010, intravitreous injections of anti-VEGF are currently first-line therapy for most eyes with visual impairment from DME. Here, we see the primary results from that study, known as Protocol I. The vertical axis represents the mean change in visual acuity from baseline and the horizontal axis shows time of follow-up in weeks. Of the primary outcome time point of 1 year, the laser treated group gained approximately 3 letters in vision from baseline. In contrast, the 2 ranibizumab-treated groups, shown in orange and blue, gained 8 and 9 letters of visual acuity. Much of the vision gain in the ranibizumab groups happened early within the first 6 months of treatment. The triamcinolone-treated eyes gained vision within the first 6 months, but then rapidly declined in vision so that they were equivalent to the laser-treated group at 1 year. This decline was often due to the
formation of cataract in these steroid-treated eyes.

Protocol I clearly established the superior efficacy of ranibizumab with either prompt or deferred laser treatment to laser therapy alone for diabetic macular edema. But how many injections are needed to achieve these results? Following the DRCR.net algorithm, the need for injections decreases dramatically over a 5-year follow-up period. Frequent, near monthly, injections are required throughout the first year of therapy. Indeed, 8 and 9 injections were given on average in the ranibizumab-plus-deferred and prompt-laser groups respectively. However, after the first 6 months in which most eyes received monthly injections, the number of injections in the second 6 months is cut in half on average to 3 and in each following year it is cut in half again, to 3 injections over the second year, followed by 2, 1 and 0 injections, on average, in years 3 through 5. As you can see, the decreasing need for anti-VEGF treatment is very different for diabetic macular edema compared with age-related macular degeneration which frequently requires chronic, possibly life-long injections.

So, this eye with visual impairment from central involved DME should likely have initial treatment with anti-VEGF injections, assuming the patient is medically stable and will be compliant with frequent visits and procedures. Once the decision is made to treat with an anti-VEGF agent as first-line therapy, the next question to then be considered is: how many initial monthly doses or loading doses should be given? The DRCR.net DME treatment algorithm calls for monthly anti-VEGF injections through the first 6 months, with 1 exception. If visual acuity is 20/20 or better and the OCT central subfield thickness is normal after the first 4 or 5 injections, further injections can be deferred, but most of the time, 6 injections are given. Let's first understand why it is important to start with 6 injections.

The number of eyes with persistent macular edema at each follow-up visit during the Protocol T study, which compared safety and efficacy of 3 anti-VEGF agents for DME, decreased over the course of time. As you can see, the number of eyes with persistent edema decreased after each subsequent injection of aflibercept throughout the initial 6 month time period from 71% to 32%. Results in this group showing decreases in persistent DME over the first 6 months with continued anti-VEGF, are similar to what was seen in the groups treated with ranibizumab and bevacizumab. Therefore, in order to give eyes the most benefit from anti-VEGF therapy, it is important to continue treating each month through 6 months. After 6 months the DRCR.net treatment algorithm moves to prn treatment.

After 6 months, here is the prn treatment algorithm that was followed in the DRCR.net studies. The eye is assessed 4 weeks after the 6 month injection. If there is change in the DME status, as measured by a 10% or more change in OCT central subfield thickness or 5 letters or more change in visual acuity testing, the eye is reinjected and the patient should return for follow-up in 4 weeks. The eye is injected each month as long as there is either improvement or worsening in retinal thickness or visual acuity.
Once an eye does not meet the threshold for change, it is considered stable, and we ask the question: has the eye been stable for at least 2 injections? If not, the eye is injected again. However, if the eye has been stable for 2 or more injections, meeting a definition of sustained stability, we start to defer injections. Stopping treatment in an eye with edema that is not continuing to improve does not mean stopping forever. If the visual acuity or OCT worsens after discontinuing treatment, then injections are resumed until there is again stability or resolution of edema. For eyes that have been stable 12 months after starting treatment, not only is the injection deferred, but follow-up can be extended to 2 months. If the eye continues to remain stable 2 months later, follow-up is then extended to 4 months. So, after 6 loading doses, if there is persistent, but stable, diabetic macular edema, injections are deferred unless the visual acuity or the OCT central subfield thickness worsens. Starting at 12 months, visit frequency is reduced to up to every 4 months provided there is no worsening at follow-up visits.

Some people have asked the question: Is it safe to withhold anti-VEGF treatment for eyes with persistent, but stable DME? Outcomes from Protocol T show what happens if one stops anti-VEGF treatment when DME is persistent, but stable after 6 months, and the eye is not switched to another therapy, such as corticosteroids.

Here we see all eyes with persistent central involved diabetic macular edema through 6 months in the Protocol T study. At 1 year, approximately 80% of these eyes still have persistent thickening. However, at 2 years of follow-up, the rates of persistent thickening were reduced in all treatment groups, so that only 44%, 68% and 54% of eyes in the aflibercept, bevacizumab and ranibizumab groups, respectively, still had thickening that persisted from the 6 month visit. So rates of thickening do not increase, but rather continue to decrease over time when using a retreatment algorithm that defers anti-VEGF treatment when DME is persistent, but stable after 6 months.

The Protocol T data also suggests that many eyes with persistent DME at 24 weeks have substantial gains in visual acuity with average gains of 8 to nearly 10 letters of vision by 2 years across the 3 treatment groups. Rates of 10 or more letter vision gain ranged from 37 to 47% and very few eyes lost 10 or more letters of vision in each treatment group. Although vision gain at 2 years is not as frequent for these eyes with persistent DME, versus those that have resolved DME at 24 weeks in the aflibercept and ranibizumab groups, the overall visual outcomes are still excellent for many eyes.

Finally, which anti-VEGF agent will be given with this regimen? Well, as mentioned, the DRCR.net defer-and-extend regimen was tested in a comparison of 3 anti-VEGF agents for DME in Protocol T. In this protocol, study participants were randomly assigned either to aflibercept, bevacizumab or to 0.3 mg ranibizumab. There was excellent follow-up through 2 years. Before the study started, it was thought that there might be a difference in response to treatment in eyes with only mild visual...
impairment and visual acuity of 20/32 or 20/40 versus those with more severe visual impairment and vision of 20/50 or worse. Indeed, the study results suggest that treatment effects differ substantially between these groups. So we will look at the results for each visual acuity group separately. When the baseline visual acuity was 20/32 to 20/40, on average, there was essentially no difference in the mean visual acuity changes from baseline to 1 and 2 years when comparing results from the defer-and-extend treatment regimen with bevacizumab, ranibizumab or aflibercept. No difference between the treatment groups was identified at the 2-year time point or when looking at average vision over 2 years. However, when the baseline visual acuity was 20/50 or worse, which was true for about half the cohort in this trial, on average the visual acuity gains were greater for eyes treated with aflibercept than either bevacizumab or ranibizumab at 1 year. And the average visual acuity change at 2 years was greater for aflibercept than bevacizumab. When we consider the average vision over 2 years using an area under the curve analysis, in eyes with worse baseline vision, aflibercept was superior to both bevacizumab and ranibizumab. On average, aflibercept-treated eyes gained 17 letters or 3.5 lines of vision as compared to the 14 and 12 letters gained by the ranibizumab and bevacizumab-treated eyes, respectively. Rates of 3 line vision gain or more were higher in the aflibercept group than the bevacizumab group. Still, it is important to recognize that many eyes in each of the 3 groups gained substantial amounts of vision over 2 years with 3 lines or more of vision gain in over 40% of the bevacizumab group. These data overall demonstrate the excellent efficacy of all 3 anti-VEGF agents for treatment of diabetic macular edema. Higher rates of laser treatment were performed in the bevacizumab group than in the other 2 treatment groups, and this is because bevacizumab was not as successful at thinning the macula than the other 2 agents. No differences were noted with respect to prespecified ocular adverse events among the 3 agents, as shown here. No differences were noted with respect to prespecified ocular adverse events among the 3 agents. On the whole, intravitreous anti-VEGF is well tolerated with low rates of ocular adverse events, including endophthalmitis and ocular inflammation among all 3 treatment groups. When looking at prespecified APTC or antiplatelet trialists collaboration adverse events for 2 years, these were noted to be different among the 3 agents with a higher percentage, 12%, experiencing these events in the ranibizumab-treated group in comparison to 8% in the bevacizumab group and 5% in the aflibercept group. After careful review of the data, the DRCR Network investigators concluded that the differences in APTC events in this trial may be due to chance alone. Rates of APTC events have varied widely between trials and eyes with diabetic macular edema. The 12% rate of APTC events in ranibizumab-treated patients in Protocol T was higher than the 2.4% seen in the RISE trial using 0.3 mg of ranibizumab and also higher than the 8.8% in the RIDE trial using 0.3 mg of ranibizumab. However, the 12% rate of APTC events with ranibizumab in Protocol T was also lower.
than the 13% rate experienced by the control group in Protocol I, which received no anti-VEGF therapy. Because of this variability in event rate across trials, driven by very small differences in absolute numbers of APTC events, the DRCR Network believes that the differences noted in Protocol T among the anti-VEGF agents, do not necessarily mean that use of ranibizumab truly leads to a greater chance of APTC events than bevacizumab or aflibercept in this cohort.

In summary, coming back to our patient with diabetic macular edema with 462 microns of central retinal thickening and 20/63 visual acuity, what should our treatment algorithm be? How many loading doses are part of the DRCR.net treatment algorithm? Six monthly injections are given unless the retinal thickening returns to normal and the visual acuity becomes 20/20 or better. In that case, the injections can be withheld unless the edema or acuity worsens again. If the edema persists after the initial 6 doses, what treatment should be given at this point? Well, anti-VEGF injections are continued monthly since many eyes, even those with previously persistent DME will continue to improve with each month of additional anti-VEGF therapy. However, once edema and visual acuity normalize or become stable for 2 consecutive visits, injections are deferred. This is done even in the setting of persistent DME, since many eyes that have persistent DME in which injections are deferred still maintain their vision gains. The benefits of switching to a different anti-VEGF agent or using different treatments such as steroids are unknown at this time. The DRCR Network treatment algorithm allows for additional focal grid macular laser, if indicated. After month 12, if injections are being deferred, visit follow-up periods can be doubled to a maximum of every 4 months. Which anti-VEGF agent should be considered as first-line therapy? All 3 are safe and are effective for treatment of DME. However, in eyes with visual acuity of 20/50 or worse, the clinical trial results indicate that aflibercept is associated with better average visual acuity results at the end of 2 years compared with bevacizumab and result in better average visual acuity over the entire 2 year span compared with both bevacizumab or ranibizumab. The DRCR.net clinical trials show that using this anti-VEGF treatment algorithm for diabetic macular edema result in excellent visual acuity outcomes over the long-term for many patients.

Congratulations, you have successfully completed the module on DRCR Network, Diabetic Macular Edema Treatment in the 21st Century.

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