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Laser Versus Anti-VEGF Injections

A patient-specific approach may increase positive outcomes.

BY VICTOR CHONG, MD

This case involves a 28-year-old man who has type 1 diabetes and severe nonproliferative diabetic retinopathy. I asked the patient to return for follow-up in 3 months. Two years later, the patient returned with early neovascularization of the disc (NVD) with 20/20 visual acuity (Figure 1). What are you going to do?

Protocol S

We have the data from the US-based Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol S trial.[1] The trial involved real-life patients from private, academic, and multicenter settings. It compared ranibizumab (n = 191; Lucentis; Genentech) with panretinal photocoagulation (n = 203; PRP) in a randomized controlled trial. Most patients had type 2 diabetes (ranibizumab: 73% vs PRP: 76%), about half in each group were white, and slightly less than half were women (ranibizumab: 43% vs PRP: 45%).

Their A1C levels are not well controlled: the median A1C levels are 8.6 for the ranibizumab group and 8.9 for the PRP group, which is to be expected from patients with long-term diabetes. The mean visual acuity is 20/32 (Table 1).

About a quarter of the patients have diabetic macular edema (DME) with vision loss, but I will take that 22% or 23% out of the discussion (Table 2). Those patients may already need a ranibizumab injection on baseline (to treat their DME) and thus taking this group into consideration could confuse the discussion.

In the PRP group, treatment was successfully completed in 98% of the patients, with about more than half completed in one session (Table 3). Some surgeons prefer to do more than one session

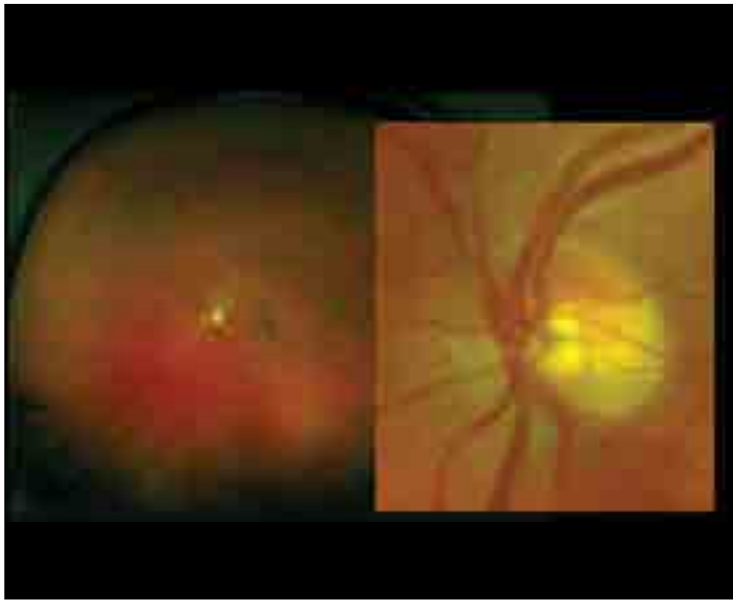

Figure 1. A patient with early NVD and 20/20 visual acuity.

TABLE 1. MEAN VISUAL ACUITY

	RANIBIZUMAB GROUP (N = 191)	PRP GROUP (N = 203)
Mean visual acuity letter score (~Snellen Equivalent)	75.0 (20/32)	75.2 (20/32)
20/25 or better	46%	46%
20/32 to 20/40	34%	33%
20/50 to 20/100	16%	17%
20/125 to 20/320	5%	4%

TABLE 2. OCULAR BASELINE CHARACTERISTICS

	RANIBIZUMAB GROUP (N = 191)	PRP GROUP (N = 203)
Mean OCT CST* (µm)	262	249
< 250 µm	66%	67%
250 to 349 µm	19%	26%
≥ 350 µm	15%	7%
Presence of central-involved DME with visual acuity loss**	Required ranibizumab at baseline	
	22%	23%

*OCT values are Stratus equivalents
**Eyes with visual acuity letter score ≤ 78 (20/32 or worse) AND OCT CST ≥ machine and gender specific thresholds

TABLE 3. PRP GROUP

	OVERALL (N = 203)
Completed initial full PRP	98%
Performed in one sitting	54%

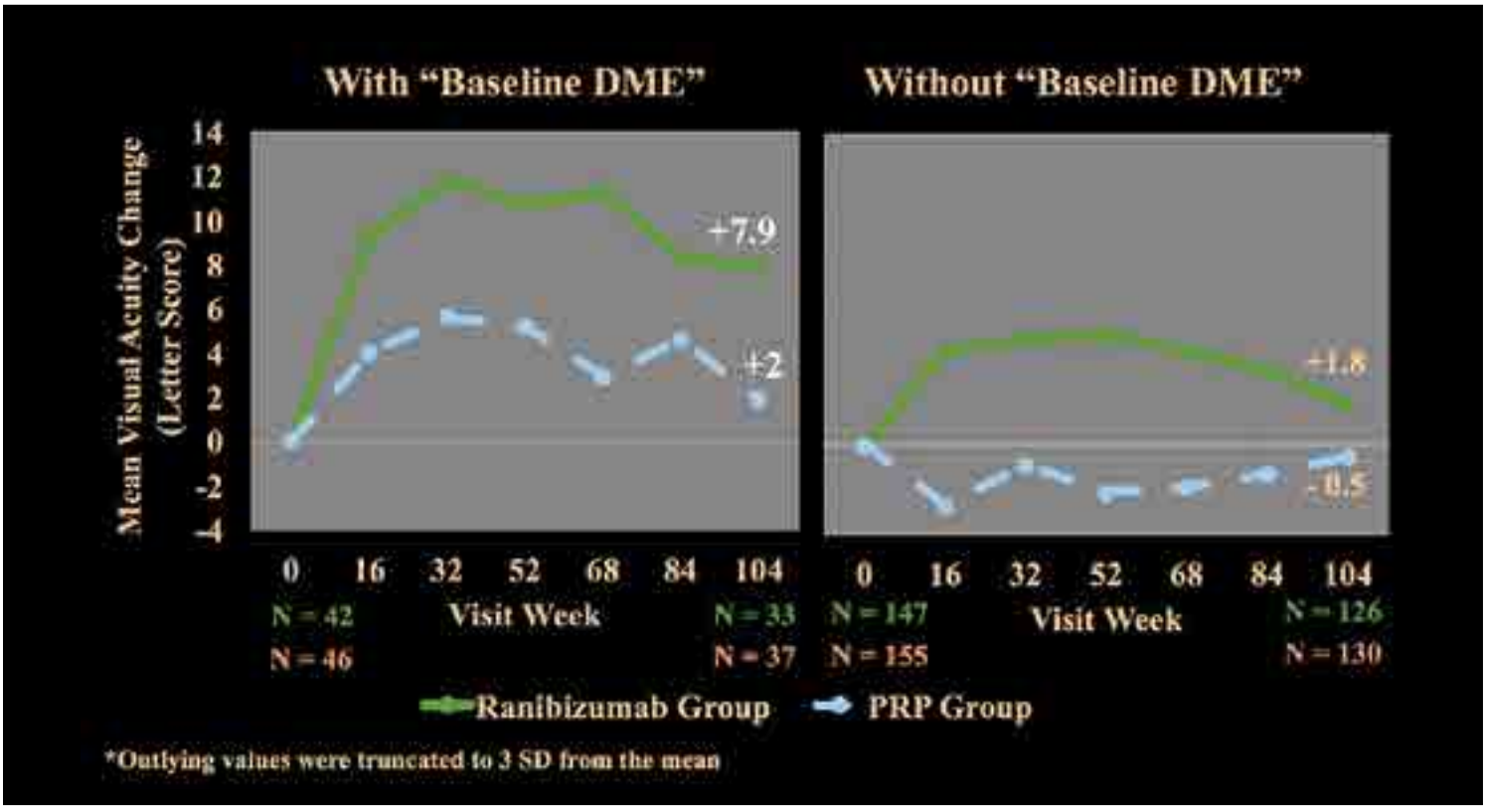

Figure 2. Mean change in visual acuity stratified by baseline DME for patients in Protocol S trial.

of PRP, but a study by Brucker showed that one session is as effective as four sessions without additional complications.[2] In the ranibizumab group, eyes without baseline DME received about 10 injections over 2 years. There were slightly better results in visual acuity with the anti-VEGF agent, but it was less than 2 letters (Figure 2). It is the results we were expecting. Whereas PRP can be performed in one or two sessions, anti-VEGF involves several injections over 2 years. Whatever treatment you choose to perform, the visual acuity difference is not significant.

The main complications of proliferative diabetic retinopathy (PDR) are retinal detachment, neovascular glaucoma, iris neovascularization, vitreous hemorrhage, and vitrectomy (Table 4). The main finding of the Protocol S trial is that there is a higher rate of vitrectomy in the PRP group compared to the ranibizumab group

TABLE 4. COMPLICATIONS OF PDR

	RANIBIZUMAB GROUP (N = 191)	PRP GROUP (N = 203)	*P* VALUE
Any retinal detachment	6%	10%	.08
Neovascular glaucoma	2%	3%	.50
Iris neovascularization	1%	1%	.96
Vitreous hemorrhage	27%	34%	.09
Vitrectomy	1%	15%	< .001

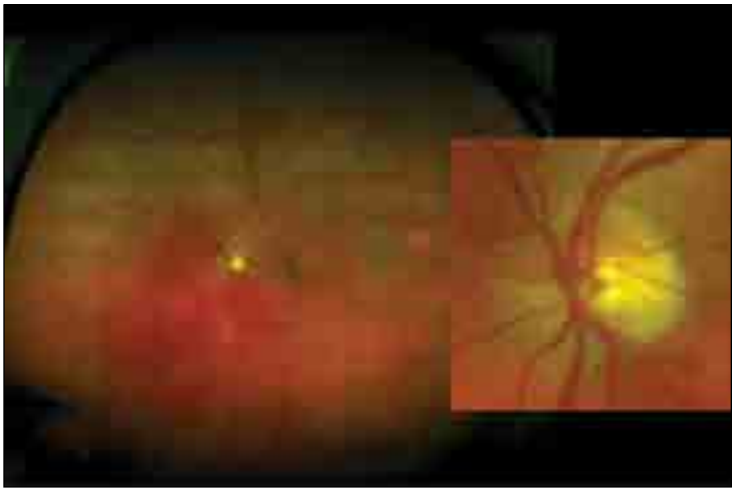

Figure 3. A patient 1 week after PRP, which induced NVD regression.

TABLE 5. DME TREATMENT THROUGH 1 YEAR: ANTI-VEGF AND LASER

	AFLIBERCEPT N = 208	BEVACIZUMAB N = 206	RANIBIZUMAB N = 206	*P* VALUE
# of Injections (Max = 13)				
Mean	9.2	9.7	9.4	
Median (25th, 75th percentile)	9 (8, 11)	10 (8, 12)	10 (8, 11)	.045†
At least one focal/grid laser	**37%**	**56%**	**46%**	<.001‡

†Global (overall 3 group comparison) *P* value. Pairwise comparisons (adjusted for multiple comparisons): aflibercept-bevacizumab: $P = .045$, aflibercept-ranibizumab: $P = .19$, bevacizumab-ranibizumab: $P = .22$.
‡Global (overall 3 group comparison) *P* value. Pairwise comparisons (adjusted for multiple comparisons): aflibercept-bevacizumab: $P < .001$, aflibercept-ranibizumab: $P = .058$, bevacizumab-ranibizumab: $P = .061$.

(15% vs 4%). However, the vitreous hemorrhage rate was not significantly different, hence, the vitreous hemorrhage in the ranibizumab group might be less severe so vitrectomy might not need surgery as often.

Patient With Early NVD

Let us go back to the patient with early NVD. I saw the patient 2 years ago and asked him to come back in 3 months, but he returned 2 years later with early NVD. It would be reasonable to give him an anti-VEGF injection that day. Protocol S showed that anti-VEGF has a lower risk of vitrectomy compared to PRP. What happens if he again returns 2 years later? The ranibizumab injection only lasts 1 or 2 months so there will likely be worsening of NVD. In this case, I performed one session of PRP instead of the anti-VEGF injection. When the patient returned for follow-up 1 week later, I was able to assess that the treatment was successful (Figure 3).

There is no doubt that anti-VEGF agents can be considered when you have a patient who is motivated. However, PRP is ideal for patients with poor compliance, and we know that among PDR patients the compliance is often poor. If a patient returns years after receiving one anti-VEGF injection, he or she may have advanced diabetic retinopathy such as tractional detachment and permanent vision loss.

Protocol T

Is there a role for laser in DME? Let us look at DRCR.net Protocol T, which compared the effectiveness of the three anti-VEGF agents: aflibercept (Eylea; Regeneron), bevacizumab (Avastin; Genentech), and ranibizumab.[2] I want to point out that about 40% of the patients in this study had prior laser. Even more interesting is that about 40% to 60% of patients who received 9 to 10 anti-VEGF injections in the first year of the study also received laser (Table 5). Therefore, I do not think that the macular laser is becoming obsolete. Nowadays, there are efficient subthreshold laser therapies such as 577 nm MicroPulse that circumvent the known drawbacks of thermal laser in treating DME. If a patient has a thick retina, then ranibizumab will likely provide a significant improvement. However, the benefit is much smaller for those with thin retinas. For those who have never had laser, I suggest a combination of laser with ranibizumab. This is not recommended for every patient, but a treatment-naïve patient may have positive results with combination therapy.

Conclusion

In summary, PRP is useful, especially in patients with PDR. Laser is still useful for early DME. A combination therapy of PRP and an anti-VEGF agent may be useful in treatment-naïve patients with DME. ■

1. Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: A randomized trial. *JAMA*. 2015;314(20):2137-2146.
2. Brucker AJ, Qin H, Antoszyk AN, et al; Diabetic Retinopathy Clinical Research Network. Observational study of the development of diabetic macular edema following panretinal (scatter) photocoagulation given in 1 or 4 sittings. *Arch Ophthalmol*. 2009 Feb;127(2):132-140.
3. Wells JA, Glassman AR, Ayala AR, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 201526; 372(13):1193-1203.

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