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# Updates in Management of Diabetic Eye Disease: Protocol S, CLARITY, and PANORAMA

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Nearly 50% of patients with high-risk proliferative diabetic retinopathy (PDR) have severe vision loss within 5 years, making diabetic retinopathy a leading cause of vision loss in patients with diabetes mellitus.[1] However, treatment with panretinal photocoagulation (PRP) can substantially reduce this risk, lowering the rates of severe vision loss by 50%.[2] As such, PRP is

the long-standing standard of care for the treatment of patients with high-risk PDR. Nonetheless, the benefits of PRP must be balanced against the following undesired side effects: peripheral field loss, decreased night vision, reduced sensitivity to contrast and color, and increased incidence of diabetic macular edema (DME).[3-5]

As anti–vascular endothelial growth factor (VEGF) agents entered the fray of diabetic eye disease management by revolutionizing the treatment of DME, they also showed their potential application for diabetic retinopathy by reducing the risk for progression and increasing the likelihood of regression.[6,7] Although intravitreal injections of anti-VEGF agents can be associated with rare, serious complications, they are typically well tolerated and thus provide a compelling potential alternative to PRP for PDR management.

## Protocol S

To that end, Protocol S of the Diabetic Retinopathy Clinical Research Network directly compared PRP with ranibizumab injections for treatment of PDR in 394 eyes of 305 patients across 55 sites.[8] None of the eyes had prior PRP, and all eyes were randomized to either PRP or ranibizumab.[8] The enrollment of both eyes was allowed (89 patients), with 1 eye in each group.[8] The study was a 2-year trial, with a primary endpoint of the mean best-corrected visual acuity (BCVA) change at 2 years and a noninferiority margin of 5 letters.[8]

Eyes randomized to the PRP group received laser treatment at baseline and were followed at 16-week intervals.[8] Additional PRP was applied if neovascularization (NV) progressed.[8] Eyes in the ranibizumab group received a 0.5-mg dose at baseline and every 4 weeks thereafter, up to week 12.[8] After the fourth dose of

ranibizumab, further doses were given at weeks 16 and 20 if any NV was still noted.[8] At week 24, eyes were examined for resolution or stability of NV.[8] Neovascularization was deemed stable in the absence of improvement or worsening after 2 consecutive injections.[8] Ranibizumab treatment was continued as needed at 4-week intervals until NV resolved or stabilized, and treatment was resumed with subsequent NV worsening.[8]

Panretinal photocoagulation was used in carefully defined cases of treatment failure or futility. The latter was declared with persistent or recurrent NV after 18 months of treatment, with at least 5 ranibizumab injections in the past 6 months.[8] Treatment failure occurred in the setting of increased NV from baseline after 4 monthly treatments, onset or increased NV of the angle, or worsening NV after injection that the investigator believed

presented a likely threat of substantial vision loss within 1 week.[8] As a result, PRP was performed in 6% of eyes in the ranibizumab arm.[8]

To address DME, defined as an increase in central subfield thickness on optical coherence tomography of at least 2 standard deviations, coupled with a BCVA of no more than 78 letters (about 20/32 VA), ranibizumab (0.5 mg) treatment was allowed in both arms.[8] Consequently, 35% of eyes in the PRP arm found to have DME at baseline were injected.[8] Additional ranibizumab and/or focal laser photocoagulation was permitted in either arm at the discretion of the investigator, leading to an additional 18% of eyes in the PRP group receiving anti-VEGF therapy.[8]

At year 2, the ranibizumab group gained 2.8 letters of BCVA compared with 0.2 letters in the PRP group ($P$<.001), meeting the primary endpoint of VA noninferiority between the groups.[8] Both the rate of VA gain and loss were similar, without statistically significant differences.[8] Forty-three percent of ranibizumab-treated eyes gained ≥10 letters of BCVA versus 36% of eyes in the PRP group (analysis limited to 167 eyes with baseline vision, allowing a 10-letter gain to remove the ceiling effect).[8] As for VA decline, 9% and 8% of the ranibizumab-treated eyes lost ≥10 letters and ≥15 letters, respectively, compared with 14% and 10%, respectively, in the PRP group.[8]

Apart from DME, the rate of other adverse events was also similar between groups.[8] Vitreous hemorrhage developed in 27% of eyes in the ranibizumab arm compared with 34% in the PRP arm.[8] Retinal detachment was uncommon, seen in 6% of

ranibizumab-treated eyes versus 10% of PRP-treated eyes.[8] As such, there was no statistically significant difference in the rate of either complication with regard to treatment.[8] However, the cumulative probability of developing DME by trial's end was statistically lower in the ranibizumab group (9% vs 28%; $P<.001$), as one might expect in an arm receiving frequent anti-VEGF therapy.[8]

In summary, Protocol S was a randomized, 2-year trial that showed the benefit of anti-VEGF treatment, specifically ranibizumab, in eyes with PDR. As with any trial, there were limitations. The inclusion of eyes agnostic of their DME status led to a significant portion of eyes receiving ranibizumab at baseline in the PRP group (35%).[8] Coupled with the as-needed treatment of eyes that eventually developed DME during the 2 years of the trial, 53% of eyes in the PRP group received ranibizumab.[8] In

contrast, only 6% of eyes in the ranibizumab arm received PRP.[8] As a result, rather than a comparison of ranibizumab with PRP as monotherapies, Protocol S could be considered a comparison of ranibizumab with PRP plus as-needed ranibizumab.[8] Also, although the exclusion of eyes with prior PRP helped to keep the direct comparison of anti-VEGF to PRP from becoming even more challenging, it limited the applicability of the results to treatment-naive patients with PDR. Nevertheless, Protocol S remains one of the first robust trials that prospectively demonstrated the efficacy of an anti-VEGF agent in the setting of PDR.

## Clarity

To complement Protocol S results, the CLARITY trial compared aflibercept with PRP in 232 patients with PDR at 22 centers in the United Kingdom, with a primary outcome of change in BCVA

at week 52.[9] Eyes with any ocular condition affecting VA, including center-involved DME (central subfield thickness ≥300 μm on optical coherence tomography), were excluded.[9] However, eyes with prior PRP were allowed if they had persistent neovascular activity requiring additional treatment.[9]

Patients were randomized to either the aflibercept or the PRP arm.[9] Both groups received the first treatment at baseline, with eyes in the aflibercept arm receiving 2 additional aflibercept injections at 4-week intervals.[9] At week 12, both arms were assessed for retreatment according to the following 3 categories: no, partial, or total NV regression.[9] Eyes in the aflibercept arm needing retreatment were given as-needed injections every 4 weeks, and as-needed laser photocoagulation was given every 8 weeks in the PRP arm.[9]

Eyes with previous PRP in both groups showed a trend toward less treatment (123 of 232).[9] The aflibercept group received an average of 4.4 ± 1.7 injections, and only 2% required supplemental PRP.[9] In that arm, PRP-naive eyes and those that had previous laser treatment received 4.6 ± 1.6 and 4.1 ± 1.8 aflibercept injections, respectively.[9] In the PRP group, 65% of eyes underwent an average of 1.17 ± 1.16 additional laser treatments.[9] Eyes without PRP prior to baseline had 1.35 ± 1.28 treatments, whereas eyes with prior PRP needed only 0.96 ± 0.96 treatments.[9]

Because patients with DME were excluded from the trial, baseline BCVA was already excellent (81.4 letters: about 20/25 VA).[9] However, eyes in the aflibercept arm gained approximately 1.5 letters of BCVA by week 12 and 1 letter by week 52,[9] which was statistically significant compared with the BCVA loss of

nearly 1 letter (*P*=.01) and 3 letters (*P*<.0001) in the PRP group at weeks 12 and 52, respectively.[9] Consequently, CLARITY exceeded its primary endpoint of BCVA noninferiority by showing the superiority of aflibercept over PRP.[9]

Other, secondary VA endpoints showed similar rates of improvement in both arms, with 5% of eyes gaining ≥10 letters of BCVA in the aflibercept group compared with 2% in the PRP group (*P*=.45; analysis limited to 196 eyes with baseline vision allowing a 10-letter gain).[9] However, rates of VA loss diverged.[9] Although the rate of a ≥15-letter loss was balanced (5% for aflibercept vs 6% for PRP; *P*=.72), the rate of a ≥10-letter loss was significantly lower in the aflibercept group (5%) than in the PRP group (15%; *P*=.009).[9]

Anatomical endpoints also favored the aflibercept group.[9] Fewer eyes in the aflibercept group continued to be graded as PDR (78%) compared with eyes in the PRP group (90%; *P*=.016), with an additional 30% of aflibercept eyes showing total regression of NV compared with the PRP group (*P*<.0001).[9] Vitreous hemorrhage, either new or increased, occurred in 9% of eyes in the aflibercept arm compared with 18% of eyes receiving PRP (*P*=.034).[9] Although the rates of vitreous hemorrhage requiring vitrectomy were too low to achieve statistical power, the trend also favored the injection group, with 1% of patients receiving aflibercept having surgery compared with 6% of patients who received PRP (*P*=.066).[9] The rate of DME onset was also lower in aflibercept-treated eyes (11%) versus PRP-treated eyes (29%).[9]

In short, CLARITY not only corroborated the noninferiority of anti-VEGF therapy to PRP seen in Protocol S but also showed the superiority of anti-VEGF in the treatment of PDR with 3 initial monthly doses of aflibercept and an average of 1.4 additional as-needed doses over 52 weeks.[9] By including eyes with prior PRP treatments and excluding those with DME, in direct contrast to Protocol S, CLARITY expanded the applicability of the results of both trials when considered jointly. CLARITY also represents a more direct comparison of anti-VEGF with PRP because only 2% of the aflibercept group received PRP, and none of the eyes in the PRP group received aflibercept.[9] However, these advantages of CLARITY come with a caveat: the VA outcomes favoring aflibercept may be rooted in its approach to DME during the trial. If as-needed aflibercept had been given for the DME that developed in both arms (more commonly in the PRP arm), would the results have been different?

# PANORAMA

The favorable results for ranibizumab and aflibercept in the treatment of PDR, along with the excellent safety profile of these agents, raised the question of whether earlier anti-VEGF intervention for diabetic retinopathy could be beneficial. PANORAMA, a 2-year, randomized controlled trial, enrolled 402 patients with moderately severe to severe nonproliferative diabetic retinopathy (NPDR) without DME to address this question. One of its primary endpoints was the proportion of eyes improving ≥2 steps on the Diabetic Retinopathy Severity Scale (DRSS) at week 52, with secondary endpoints including the rate of progression to PDR and of progression to a vision-threatening complication composite endpoint of PDR or anterior segment NV.[10] Patients were randomized to 1 of 3 arms:

aflibercept 2 mg every 16 weeks (after 3 monthly doses followed by one 8-week dose), aflibercept 2 mg every 8 weeks (after 5 monthly doses), or sham.[10]

At week 52, 65% of eyes in the every-16-week and 80% of eyes in the every-8-week aflibercept groups showed a ≥2-step improvement on the DRSS compared with only 15% of eyes in the sham group (*P*<.0001 for both).10 Moreover, 9% of the every-16-week group and 15% of the every-8-week group had a ≥3-step improvement versus <1% of the sham group (*P*<.001).[10] Only 2% of eyes in the every-16-week and 0% in the every-8-week aflibercept group developed PDR compared with 12% of eyes in the sham group (*P*<.01).[10] As for the vision-threatening complication endpoint, only 4% of patients in the every-16-week group and 3% of patients in the every-8-week group had that outcome compared with 20% of patients in the sham group

(*P*<.0001 for both), resulting in a risk reduction of 85% to 88%.[10] The incidence of center-involved DME was also reduced by 73% to 79%, with rates of 7% in the every-16-week and 8% in the every-8-week groups compared with 26% in the sham group (*P*<.001 for both).[10]

At week 100, the rate of ≥2-step DRSS improvement remained stable in the every-16-week group, going from 65% to 62%, with an average of 2.6 additional injections of a possible 3.[11] The every-8-week group, having shifted to an as-needed schedule in year 2, received an average of 1.8 injections of a possible 6 and had a decline in ≥2-step DRSS improvement as a result (from 80% to 50%).[10] Overall, 92% of patients who achieved a ≥2-step improvement in DRSS maintained that improvement with less-frequent dosing by week 100.[10]

# Summary

PANORAMA represented the logical progression of the Protocol S and CLARITY trials that, when combined, help to usher in a new treatment paradigm for diabetic eye disease. Although the benefit of PRP in PDR has been established for decades2 and anti-VEGF therapy has similarly become the gold standard for eyes with DME, resulting in de facto treatment of NPDR when associated with DME,[12,13] the role of anti-VEGF agents in the setting of diabetic retinopathy without DME has been uncertain. However, the results of Protocol S,[8] CLARITY,[9] and more recently PANORAMA[10] present a compelling argument for the strategic use of anti-VEGF agents in treating patients with diabetic retinopathy, from moderately severe NPDR to PDR, independent of DME status. By incorporating these anti-VEGF algorithms into

our approach to diabetic eye disease, there is hope that we can reduce the dire consequences of diabetic retinopathy in our patients.

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