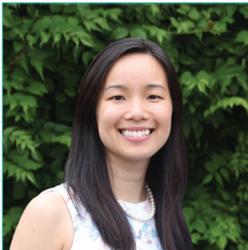


# Combination Treatment of Diabetic Macular Edema with Anti-Vascular Endothelial Growth Factor and Steroids: Analysis of DRCR.net Protocol U

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## ABSTRACT

Diabetic macular edema (DME) is the main cause of visual impairment in diabetic patients. Intravitreal anti-vascular endothelial growth factor (VEGF) therapy is considered the first-line treatment option in the management of DME with corticosteroids used as second-line therapy. The DRCR.net Protocol U study was a Phase II trial that sought to compare the combination of a steroid and anti-VEGF therapy to anti-VEGF monotherapy regarding visual acuity and anatomic outcomes. This review highlights the strengths, weaknesses, and clinical implications of this study.

**Keywords:** Corticosteroids, Diabetic macular edema, Protocol U

## INTRODUCTION

Diabetic macular edema (DME) is the most common cause of vision loss in patients with diabetes, with a reported cumulative 25-year incidence of 29% of type 1 diabetics according to the Wisconsin Epidemiologic Study of Diabetic Retinopathy.<sup>[1,2]</sup> It is characterized by capillary leakage, fluid accumulation, and macular thickening

following the breakdown of the blood-retinal barrier.<sup>[3]</sup> Vascular endothelial growth factor (VEGF) is a key contributor to the development of DME by increasing permeability of the retinal vessels.<sup>[4]</sup> Consequently, intravitreal anti-VEGF therapy is the first-line treatment option in the management of DME and is effective in reducing the central retinal thickness and improving best-corrected visual acuity (BCVA) in patients with DME.<sup>[5]</sup>

Although anti-VEGF monotherapy is effective as a treatment for most patients with center-involved DME, a significant proportion of patients have a suboptimal response to treatment. In Protocol I, approximately 40% of ranibizumab-treated eyes had persistent macular thickening after 1 year of monthly injections.<sup>[6]</sup> In the RISE and RIDE studies, macular edema persisted in approximately 23% of patients

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after 2 years of monthly ranibizumab injections, and 40% of patients had not achieved a BCVA of  $\geq 20/40$ .<sup>[5]</sup>

Inflammatory mediators and pathways appear to also be involved in the development of DME, and it may be important to treat this component in patients who do not respond to anti-VEGF therapy. Corticosteroids have reemerged as an alternative therapy for persistent DME or refractory to anti-VEGF monotherapy. Corticosteroids have a broad spectrum of biologic action, including downregulation of inflammatory cytokines and growth factors such as VEGF,<sup>[7]</sup> and enhancement of the barrier function of vascular tight junctions.<sup>[8,9]</sup> Although intraocular corticosteroids are associated with cataract formation and elevated intraocular pressure (IOP) for some patients, they have been shown to lower the central subfield thickness and improve visual acuity for suboptimal responders to anti-VEGF.<sup>[10,11]</sup>

There are now several different steroids and delivery mechanisms available for DME. Prior studies have examined the beneficial effects of triamcinolone for DME.<sup>[12]</sup> Dexamethasone has been shown to be more potent with theoretically fewer steroid complications, compared to triamcinolone in *in vitro* studies.<sup>[13]</sup> The dexamethasone intravitreal implant (Ozurdex, Allergan, Irvine, CA) is currently approved by the US Food and Drug Administration for the treatment of DME, macular edema associated with retinal vein occlusion,<sup>[14]</sup> and noninfectious posterior uveitis.<sup>[15]</sup> It delivers a potent corticosteroid through a biodegradable polymer that releases the medication in a sustained and safe dose over several months.<sup>[9]</sup> The Macular Edema: Assessment of Implantable Dexamethasone in Diabetes (MEAD) study showed that dexamethasone intravitreal implant improved vision in patients over a 3-year period, compared to sham.<sup>[10]</sup> Patients' vision improved overall by 4 letters and pseudophakic patients improved by 6 letters over a year period.

Combination therapy consisting of an anti-VEGF agent and a corticosteroid may have a synergistic effect by reducing levels of VEGF, cytokines, and other inflammatory mediators. Several studies have shown that combination treatment with bevacizumab (Avastin; Genentech, South San Francisco, CA) and triamcinolone is possible with good outcomes.<sup>[16,17]</sup> Because corticosteroids consistently reduce retinal thickening, the addition of a steroid might benefit patients with persistent DME and vision loss despite treatment with an anti-VEGF agent. The recent DRRC.net Protocol U study sought to compare the combination of a steroid and anti-VEGF therapy to anti-VEGF monotherapy regarding visual acuity and anatomic outcomes.

## DRRC.NET PROTOCOL U

Protocol U was a multicenter, phase 2, randomized clinical trial evaluating a combination of dexamethasone and

ranibizumab (Lucentis; Genentech, South San Francisco, CA) versus ranibizumab monotherapy for the treatment of persistent center-involving DME. The study was funded by the National Eye Institute, Allergan, and Genentech and involved forty clinical sites.

The study involved 236 eyes who had persistent DME despite receiving at least three anti-VEGF injections within 20 weeks of study enrollment. To ensure that enrolled eyes truly had persistent DME, patients were entered into a run-in phase in which they were treated with 3 month injections of ranibizumab. At the end of the run-in phase, there were 129 eyes with persistent edema who were randomized to receive either the intravitreal sustained dexamethasone implant, 700  $\mu\text{g}$ , injection or sham treatment, both in addition to continued 0.3 mg ranibizumab treatment as often as every 4 weeks. Retreatment with ranibizumab occurred as often as every 4 weeks if the Snellen equivalent was 20/25 or worse or if there was persistent edema. The combination arm was eligible for a second dexamethasone implant beginning at 3<sup>rd</sup> month and patients were followed to week 24.

The primary outcome for efficacy was mean change in BCVA from baseline to the 24-week visit. The secondary endpoint was central subfield retinal thickness, as measured by optical coherence tomography at 24 weeks. Among the 129 eyes, 65 eyes underwent combination treatment and 64 had ranibizumab alone. At 24 weeks, results showed no significant difference in visual acuity outcome between the two treatment arms, with mean improvements of 2.7 letters in the combination arm and 3.0 letters in the ranibizumab monotherapy arm (adjusted group difference, 0.5 letter;  $P = 0.73$ ).

However, anatomic outcomes did differ between the treatment groups, with the combination group having a significantly greater reduction in retinal thickness, with mean central subfield thickness decreases of 110  $\mu\text{m}$  with combination therapy compared to 62  $\mu\text{m}$  with monotherapy ( $P < 0.001$ ). Furthermore, 52% versus 31% of patients in the combination versus monotherapy arms had a resolution of DME.

## CONSIDERATIONS

### Strengths

There were many strengths to the study including its randomization and masking of participants to avoid bias. There was also a clearly defined run-in phase that identified eyes that were more likely to have truly persistent DME despite anti-VEGF therapy. Participants had at least 3 anti-VEGF injections before they were considered to have persistent DME, and they were given 3 additional ranibizumab injections during the run-in phase. This addresses potential

concerns that suboptimal responses were initially a result of insufficient anti-VEGF treatment.

The high retention rate was also a strength. All patients in the monotherapy group completed the 24-week visit as did 97% of patients in the combination group.

## Weaknesses

While the run-in phase attempted to identify study eyes that truly had persistent DME despite anti-VEGF therapy, approximately half of subjects received only 3 anti-VEGF injections before the run-in phase. Therefore, many subjects in the combination group received only a total of 6 anti-VEGF treatments before dexamethasone therapy. This group did not achieve visual acuity gains compared to subjects who had a longer duration of anti-VEGF before enrollment. The relevance of this finding is limited by the small sample size.

In any study involving steroids, cataract progression can skew visual acuity results. The original trial design included only patients with pseudophakic eyes because of corticosteroids' known effect on cataract progression. However, because of slow patient accrual in the study, investigators modified the design to allow inclusion of phakic eyes. The investigators do indicate that 6 months is likely not enough time for visually significant cataract formation but is a factor worth considering. Results of a preplanned subgroup analysis of BCVA outcomes based on phakic status did show that the subgroup of pseudophakic eyes had a trend toward improved visual acuity outcomes for the combination arm (adjusted difference: +3.1 letters for pseudophakic eyes vs. -3.0 letters for phakic eyes). However, Protocol U was not sufficiently sized to determine if pseudophakic patients would have greater functional benefit with combination treatment. The finding was based on small between-group differences and relatively small numbers, and this difference approached but did not meet, statistical significance ( $P = 0.08$ ).

## Continued improvement with anti-VEGF

Following the run-in phase of Protocol U, approximately one-third of eyes became ineligible for randomization into the trial because their persistent DME resolved. This suggests that some may require six or more anti-VEGF injections, likely monthly, before visual and/or anatomic improvement is seen. Such improvement is in line with prior studies which showed that eyes with persistent DME after 6 months continued to improve beyond 3 injections.<sup>[6]</sup>

However, previous DRCR.net studies have shown that some patients are early, fast responders to treatment, and others are slow responders.<sup>[18]</sup> Patients in the RISE and RIDE trials who were initially treated with sham injections before crossing over to ranibizumab treatment did not experience similar

visual acuity gains as those patients receiving ranibizumab immediately.<sup>[19]</sup> This suggests that delayed initiation of effective treatment may adversely affect vision and limit visual acuity potential. Thus, there may be a need to treat DME promptly and to determine optimal treatment regimen early in the disease course. Early identification of slow responders to anti-VEGF agents may be key to successful treatment of DME.<sup>[20]</sup>

## Correlation between central retinal thickness and visual acuity

Although it is well established that treatments that reduce DME can improve or stabilize visual acuity, the results of Protocol U suggest that reduced central retinal thickness may not correlate with improved visual outcomes. Previous studies have shown that retinal thickness on optical coherence tomography correlates poorly with visual acuity and that there can be substantial variation in visual acuities at any given retinal thickness for DME.<sup>[12,21]</sup> This suggests that optical coherence tomography (OCT) measurement alone may not be a good surrogate for visual acuity in DME. Assessment of macular thickness using OCT is clinically useful, but macular thickness is just one of several variables affecting visual acuity. Analysis of other factors including integrity of the outer segment, the external limiting membrane and ellipsoid zone as predictors of visual outcome in eyes with DME, as well as other biomarkers, may serve as better surrogates measure of visual function in future trials of DME.

## Safety signals

The safety profile of the dexamethasone implant in this study was comparable to previous studies. Combination treatment led to increased IOP or initiation of antihypertensive eyedrops in 19 (29%) eyes, as compared with none in the group that received ranibizumab injections alone ( $P < 0.001$ ). This is comparable to the MEAD study in which approximately a third of patients had clinically significant increased IOP while on dexamethasone treatment administered every 6 months.<sup>[10]</sup> The DEX implant has been associated with a lesser incidence of increases in IOP compared with the fluocinolone acetonide implant devices and 4 mg intravitreal triamcinolone.<sup>[22]</sup> Less is known in comparison to 2 mg triamcinolone.<sup>[23]</sup> Side effects of ocular hypertension are generally manageable with medication or no therapy with rare patients requiring trabeculoplasty or incisional glaucoma surgery. In the MEAD trial, incisional glaucoma surgery was required in 0.6% of patients with DME treated with the 700 µg dose of the dexamethasone intravitreal implant in 3 years. No patients required incisional glaucoma surgery in Protocol U, but longer-term data would be needed to determine the cumulative incidence of IOP-related adverse events.

Also of interest would be to assess the rates of other injection-related adverse events, such as endophthalmitis.

Clinical trials of dexamethasone therapy for DME and other conditions have reported varying rates of endophthalmitis from 0 to 1.3% of injections.<sup>[10,14,15]</sup> The rate of culture-proven endophthalmitis among eyes that received dexamethasone implant monotherapy was reported to be 0.06% of injections or 0.2% of patients.<sup>[24]</sup> No patient in either treatment group in Protocol U developed endophthalmitis. A larger cohort of patients would be useful to compare the incidence of these adverse events with findings from prior clinical studies.

### Treatment burden

The addition of the dexamethasone therapy has the potential to reduce treatment burden and the number of intravitreal injections. In the MEAD study, an average of only 4–5 injections over 3 years was needed - although this needs to be interpreted carefully because the subjects were only allowed to receive an injection every 6 months, which is less than permitted by Protocol U and real-world practice.<sup>[10]</sup> In general; however, the longer duration of action of the dexamethasone implants may allow decrease in treatment burden for patients compared with anti-VEGF monotherapy. In Protocol U, there was no difference detected, but the follow-up period was limited for such an outcome to be assessed. Future studies of longer duration would be helpful in assessing the number of injections required.

## CLINICAL RELEVANCE

Although Protocol U did not show that there was a significant visual acuity benefit to adding a dexamethasone implant to ranibizumab within the confines of the clinical trial design and follow-up period, corticosteroid therapy continues to have an important adjunctive role in the management of complex DME. Treatment duration was relatively short at 6 months. It would be interesting to see if there is any improvement in visual acuity outcomes with long-term data especially in a larger pseudophakic cohort or following cataract extraction. All benefits would have to be balanced with the possibility of ocular hypertension and associated complications.<sup>[10]</sup> Findings from these studies may further help guide corticosteroid use in the treatment of DME.

## CONCLUSION

The management of DME remains complex, and often multiple treatment approaches are needed. Despite the significantly greater reduction in retinal thickness in the combination group, adding dexamethasone to ranibizumab treatment did not lead to greater improvement in vision in patients with persistent DME compared to ranibizumab with a sham dexamethasone injection.<sup>[25]</sup> Understanding the detailed study designs of clinical trials will hopefully allow

us to recognize the strengths and limitations of the studies, as well as to identify which patients are more similar to the subjects enrolled in the studies, and which are not, to allow optimal treatment for the individual patient.

### Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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### Conflicts of interest

Dr. Yoshihiro Yonekawais is on the Editorial Board of the Journal. Yonekawa: Allergan (advisory board), Regeneron (advisory board). Ung: None. Moussa: None.

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