

# Anti-VEGF Treatment in Chronic Persistent Diabetic Macular Oedema

An Expert Interview with Kevin J Blinder

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## Kevin J Blinder

Dr Blinder is an attending physician at the Retina Institute and is Clinical Professor of Ophthalmology and Visual Sciences at Washington University School of Medicine. Dr Blinder has published over 100 articles in ophthalmologic peer-reviewed journals, along with five book chapters. He has presented at the annual meetings of the American Academy of Ophthalmology, the American Society of Retina Specialists, the Retina Society, the Macula Society and the Association for Research in Vision and Ophthalmology. He has also lectured on various topics at numerous meetings both inside and outside the United States. Dr Blinder has received numerous awards, including the Vitreous Society Honor Award, the American Academy of Ophthalmology Achievement Award and Senior Achievement Award, the National Marfan Foundation Heartworks Hero with a Heart award and the American Society of Retina Specialists Service award. He has been or is currently an investigator in over 30 clinical trials dealing with macular degeneration, diabetic retinopathy, uveitis and vitreo-retinal surgery. He serves as a reviewer for a multitude of medical journals in the field, has served on numerous boards and committees and is a past president of the St. Louis Ophthalmological Society and the American Diabetes Association. Dr Blinder is a member of the Retina Society, American Society of Retina Specialists and the Macula Society.

## Keywords

Diabetic macular oedema (DMO), persistent DME, chronic persistent DMO, anti-VEGF treatment, bevacizumab, ranibizumab, aflibercept, Ozurdex, fluocinolone

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We have seen the efficacy of anti-vascular endothelial growth factor (VEGF) therapy in the treatment of diabetic macular oedema (DMO) as demonstrated by the major clinical trials, but what do we do for those that respond poorly to the standard treatment regimen? Let's discuss this issue and others as it pertains to the treatment of DMO.

## Q. How prevalent is chronic persistent diabetic macular oedema following anti-vascular endothelial growth factor (VEGF) treatment?

To determine the prevalence of chronic persistent diabetic macular oedema (cpDMO), one must first define what is meant by cpDMO. In a post hoc exploratory analysis by the Diabetic Retinopathy Clinical Research Network (DRCR.net), authors defined persistent DMO (pDMO) as 'eyes with OCT CST [optical coherence tomography central subfield thickness] of 250 µm or greater (stratus OCT equivalence values) at all completed visits through the 24-week visit despite receipt of at least four of the potential six protocol-mandated intravitreal ranibizumab injections during this period'.<sup>1</sup> In the same paper, authors defined cpDMO as 'eyes with persistent DMO (as previously defined) that have not yet achieved a CST less than 250 µm (stratus equivalence values) and 10% or greater reduction relative to the 24-week study visit on at least 2 consecutive study visits subsequent to the 24-week visit as of a given time point'. The study evaluated ranibizumab-treated eyes from the DRCR.net trial (Protocol I) comparing laser treatment, ranibizumab and triamcinolone for DMO.<sup>2</sup> In the post hoc analysis utilising the above definitions, the incidence of pDMO was about 40% (117/296). Going forward, of these patients with pDMO, 81.1% had persistent oedema at 1 year or cpDMO. By 3 years, the percentage of cpDMO went down to 40.1%, with CST of 396 µm at baseline and 278 µm at 3 years.

## Q. Could you tell us a little about the recent post hoc analyses of the DRCR.net Protocol T clinical trials and its findings?

Similar to the post hoc analysis on the data from Protocol I, we wanted to see what the incidence was of both pDMO and cpDMO in Protocol T.<sup>3</sup> The DRCR.net Protocol T looked at all three anti-VEGF agents – bevacizumab, ranibizumab and aflibercept – in a randomised, comparative effectiveness trial in the treatment of DMO.<sup>4</sup> All three agents, on average, improved vision at 1 and 2 years, with aflibercept having a greater effect in the 20/50 to 20/320 baseline visual acuity group. In the post hoc analysis, utilising the previous definitions, pDMO at 24 weeks occurred in 31.6%, 65.6% and 41.5% of the patients given aflibercept, bevacizumab and ranibizumab, respectively. DMO was more likely to persist in the bevacizumab group than in the aflibercept or ranibizumab groups. At 2 years, the likelihood that these patients would manifest pDMO and fulfill the criteria of cpDMO was 44.2%, 68.2% and 54.5% with aflibercept, bevacizumab and ranibizumab, respectively. On the positive side, very few eyes with cpDMO lost >2 lines of vision (<3.3% in each treatment group), while a vision gain of >2 lines of vision from baseline at 2 years was common (62.1%, 51.4% and 44.7% of the aflibercept-, bevacizumab- and ranibizumab-treated groups with cpDMO respectively).

### Q. What are the treatment options for patients with chronic persistent diabetic macular oedema despite treatment?

Again, the results of the post hoc analysis of Protocol T reveals an overall good visual outcome in many patients despite cpDMO.<sup>3</sup> So the argument here would be to continue the status quo treatment regimen because in the long run these patients do better than the controls.

Another option would be to change to another anti-VEGF agent. Some insurance companies in the US mandate beginning treatment with the more economical anti-VEGF drug, bevacizumab. Yet we know that for certain subsets of patients with vision 20/50 or worse, aflibercept resulted in better visual acuity on average. The question that the DRCR.net Protocol AC is attempting to answer is what happens when one starts treatment with bevacizumab and then changes to aflibercept, if needed. Will this group of patients catch up to patients initially beginning with aflibercept therapy?

There are an abundance of smaller studies looking at the effects of switching to another anti-VEGF agent for treatment failures. Ashraf et al. looked at the effect of early switching to ranibizumab or aflibercept in DMO eyes that have shown no response to bevacizumab.<sup>5</sup> This was a retrospective analysis of 45 patients with DMO. Patients had a treatment duration of less than 9 months and were deemed non-responsive to bevacizumab if they received at least three consecutive injections and showed <10% decrease in CST on OCT. All patients then received an aflibercept or ranibizumab injection within 4–6 weeks of the last bevacizumab injection. Both switch groups demonstrated improved vision with a decrease in CST with only one injection. Further follow up was not reported.

Ferris et al. looked at the potential effect of switching anti-VEGF agents in both patients with age-related macular degeneration and patients with DMO.<sup>6</sup> For patients with DMO, the authors used data from the DRCR.net to develop clinical 'switching rules' for both 3 and 6 months after initiation of treatment. The switching rules consisted of persistent OCT thickening, vision 20/40 or worse, or <1 line gain of vision from baseline – provided they were compliant with all visits and treatments. Once these 'treatment failures' were identified, the patients were continued on their assigned ranibizumab treatment. The mean visual acuity improvement during the 3 months after the switching rules were met was 3–5 letters – which was sustained for the remainder of the study. Anatomically, the mean reduction in central retinal thickness was 40–70 µm. The authors point here was the importance of having a comparison group when evaluating the effect of switching anti-VEGF agents for the treatment of DMO.

Another option for cpDMO is intravitreal injection of corticosteroids. My steroid of choice is dexamethasone intravitreal implant (Ozurdex®, Allergan, Dublin, Republic of Ireland), which provides sustained release of dexamethasone. The MEAD (Macular Edema Assessment of Implantable Dexamethasone in Diabetes) study examined the safety and efficacy of Ozurdex in DMO.<sup>7</sup> There has been widespread acceptance of this delivery system since its release. DRCR.net looked at adding Ozurdex to the treatment regimen of ranibizumab in patients with pDMO.<sup>8</sup> This was a phase II multicenter randomised clinical trial at 40 US sites in 129 eyes. Patients underwent a run-in of three additional ranibizumab injections, then, if still eligible, were randomised to Ozurdex or sham injection with continued ranibizumab injections: 116 patients were randomised with 24 weeks follow up. The results revealed no difference in the mean visual acuity outcome of combination therapy

versus monotherapy, with a significant reduction in retinal thickness in the combination group. The BEVORDEX study compared bevacizumab with Ozurdex implant and had similar improvements in vision (40% improvement with bevacizumab versus 41% with Ozurdex).<sup>9</sup> None of the patients given bevacizumab lost vision, while 11% of eyes on Ozurdex lost 10 letters of vision or more, mainly due to cataract progression. The FAME trials (fluocinolone insert) were two parallel, prospective, randomised, phase III clinical trials evaluating sustained release fluocinolone versus control.<sup>10</sup> The study enrolled 956 patients with follow up at 2 years revealing a visual acuity gain of >15 letters in 28% of the treatment group versus 16% in the sham group. Subgroup analysis, however, revealed that those with chronic DMO (definition here was >3 years from diagnosis) did better than those with acute DMO. The safety profile is questionable, with incisional glaucoma surgery ranging from 3.7–7.6% and cataract surgery ranging from 41.1–50.9% of patients.

### Q. What advice would you give to ophthalmologists regarding switching anti-VEGF treatment?

I do not want to reiterate what I just discussed in the previous section. Suffice to say there really is an abundance of publications on the 'efficacy' of switching anti-VEGF treatment. However, in reviewing the data that I presented concerning the post hoc analyses of Protocols I and T, persistence of treatment can and will lead to further anatomic and visual improvement. Use caution when considering changing treatment strategies in this difficult subset of patients. Persistence, with whatever treatment modality, is certainly better in the long run than no treatment in the non-compliant patient due to frustration with not understanding the chronicity of their pathology. It is extremely important that our patients understand this is a chronic disease requiring a lifelong commitment to treatment.

### Q. At what stage would you change the frequency of anti-VEGF injections?

This is an extremely good question that is extremely difficult to answer. If we look at all the various studies on DMO, trying to prove efficacy and at the same time decrease the treatment burden, we keep going back to the pivotal clinical trials for the unequalled visual results. The RISE and RIDE studies that looked at ranibizumab treatment of DMO saw significant improvements in vision that were sustained with monthly injections.<sup>11</sup> It is very difficult to compare visual outcomes across studies, so I will not attempt to do that here. In Protocol T, the treatment regimen consisted of monthly injections unless visual acuity was 20/20 or better with a CST below the eligibility threshold and no improvement or worsening over the last two injections.<sup>4</sup> Beginning at 6 months, an injection was not given if there was no improvement or worsening over the last two injections either visually or anatomically. One can certainly follow this treatment protocol and apply it to real world practice. The TREX-DMO Study Group looked at monthly ranibizumab treatment of DMO, treat and extend (TREX), and treat and extend with angiography-guided macular laser (GILA).<sup>12</sup> In a prospective, multicenter trial, 150 eyes were randomised into the three treatment arms. At 1-year follow up there was no significant difference in the three groups visually or anatomically. The mean number of injections was significantly reduced in both extension groups compared to the monthly cohort. The macular laser addition did not seem to be beneficial to the overall outcome.

So, while I think there is data to support changing the frequency of anti-VEGF injections to decrease the treatment burden, one can never be faulted by continuing to follow the pivotal study protocols and maintaining monthly injections. □

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