Persistent diabetic macular edema in a ‘real world’ patient: lessons, challenges and multimodal therapy

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History:
A 58 year-old phakic woman with longstanding non-proliferative diabetic retinopathy (DR) and center-involving diabetic macular edema (DME) presented for evaluation and management following a period of poor follow-up. Prior treatment for DME included focal laser and intravitreal injections of 1.25mg bevacizumab (Avastin, Genentech, South San Francisco, CA) by an outside physician; however, her last treatment with bevacizumab was 10 months prior. The patient noted improved systemic diabetic control with a hemoglobin A1c of 7.4% on a stable diabetic medication regimen. Subjectively, the patient reported long-term poor visual acuity without recent sudden or significant change. She had no prior history of vitrectomy, proliferative DR, glaucoma, or prior ocular surgery.

Examination:
Upon initial examination, visual acuity was 20/200 in each eye. Motility, pupillary, and anterior segment examination was unremarkable except for 2+ nuclear sclerotic cataract in each eye. Funduscopic examination revealed non-proliferative DR with significant DME (Figure 1, A-B). Focal laser scarring was present within the macula. Fluorescein angiography revealed extensive exudation in both eyes (Figure 1, C-D). Spectral domain optical coherence tomography (OCT) revealed intraretinal fluid, exudates, and loss of outer retinal architecture consistent with DME (Figure 2, A-B). Following additional focal laser and a series of 6, monthly intravitreal injections of 0.3mg ranibizumab (Lucentis, Genentech, South San Francisco, CA), the DME improved yet was persistent (Figure 3, A-B). The patient was then again lost to follow-up for a period of 3 months, and her OCT appearance and visual acuity remained stable (Figure 4, A-B). Upon return, persistent DME was most notable in the right eye. Following one intravitreal injection of Ozurdex (0.7mg dexamethasone implant, Allergan, Irvine, CA) in the right eye, the DME resolved (Figure 5, A-B). Visual acuity improved to 20/100 in each eye following treatment.

Discussion:
DME is the most common cause of visual loss in working-aged patients with diabetic retinopathy in developed countries. The pathophysiology in DME is complex, but has been attributed to increased levels of growth factors, such as vascular endothelial growth factor (VEGF), and inflammatory cytokines that may vary from patient to patient. Multiple treatment options, including anti-VEGF therapy with bevacizumab, ranibizumab, and aflibercept (Eylea, Regeneron, Tarrytown, NY) and corticosteroid therapy with the Ozurdex dexamethasone implant have been evaluated in Phase III clinical trials and have demonstrated efficacy for reduction in central macular thickness (CMT) and improvement in visual acuity in patients with DME.
This patient case demonstrates a common scenario encountered in 'real world' patients with DME: periods of non-compliance with follow-up, history of multiple, non-standardized prior treatments, and later presentation. Such patient features are not well represented in the body of prospective clinical trial data in DME patients, making a preferred management strategy for patients with persistent DME unclear.

The case highlights several important points in regards to DME management. Firstly, current evidence reveals that early treatment not only results in improved visual acuity outcomes but also may reduce the number of treatments required over the long-term. In the Phase III RISE/RIDE trials, patients enrolled in the sham/rescue laser group who later crossed-over to receive ranibizumab therapy did not achieve final visual acuity gains observed in the arms receiving ranibizumab from the outset (+4.5 letters from baseline versus +10.6 letters in the 0.3mg ranibizumab group at 12 months, respectively). More recently, Wykoff et al analyzed the open label extension of the RISE/RISE trials and compared eyes requiring no further anti-VEGF treatments to those requiring >7 annual treatments. Results revealed that patients requiring >7 ongoing treatments had longer duration of DME at baseline (34.8 months vs. 25.2 months), were more likely to have proliferative DR at baseline (47.4% versus 27.3%), and less likely to achieve >2 step improvement in DR Severity Scale at 24 months (12.5% versus 21.5%) compared to eyes requiring no further treatment. The results suggested that patients with lower initial levels of DR severity and better initial response to ranibizumab had a lower frequency of anti-VEGF treatments over time, underscoring that treatment at early stages may result in reduced overall treatment burden. In this case, the patient presented with persistent disease that was, per available records and history, never fully controlled and treated after significant visual acuity reduction occurred. While subjective and objective visual acuity improvement was observed following treatment, final visual acuity was at the level of 20/100, likely owing to the loss of outer retinal architecture due to persistent fluid noted on OCT, underscoring the importance of early, effective treatment.

Secondly, evidence also notes that effective treatment for DME may be achieved with corticosteroid therapy, including at extended treatment intervals and in eyes with prior anti-VEGF treatment. In a recent study, Shah et al prospectively compared intravitreal bevacizumab monotherapy versus every-three-month intravitreal Ozurdex monotherapy for persistent DME. Similar visual acuity gains were noted between groups, but a significantly greater reduction of CMT was observed in the Ozurdex group compared with the bevacizumab group (mean final CMT 336±89 μm versus 471±157 μm, respectively, p = 0.001). In addition, the number of injections given was greater in the bevacizumab monotherapy group compared to the Ozurdex group (7.0±0.2 versus 2.7±0.5, respectively, p < 0.001). More-over, sub-group analysis of the MEAD study revealed Ozurdex therapy was effective in eyes with prior history of treatment focal laser, anti-VEGF therapy, and/or triamcinolone. In these eyes with prior treatment, 21.5% of Ozurdex treated patients versus 11.1% of sham had ≥ 15-letter BCVA gain from baseline at study.
end (p = 0.002) with re-treatment allowable no more than every 6 months per protocol. In this case, the patient noted history of non-compliance with follow-up due to struggles with office visit frequency and perceived lack of change in visual acuity with treatment. Following initiation of Ozurdex, the persistent DME resolved clinically and visual acuity slightly improved. The patient reported satisfaction with subsequent every-three-month treatment intervals/monitoring.

**Conclusion:**
Management of a patient with persistent DME despite prior therapy is a common, yet challenging, clinical scenario. In this case, use of the Ozurdex implant allowed for resolution of persistent DME in a patient with variable follow-up compliance and prior incomplete response to focal laser and anti-VEGF treatment while utilizing an extended treatment interval. The case highlights common challenges encountered in ‘real world’ patients with DME, and underscores how anti-VEGF and corticosteroid therapy may be used in combination with decisions made to tailor to individual patient needs.

With multiple treatment modalities available, including focal laser, anti-VEGF therapy, intraocular or periocular steroids, and vitrectomy, management should be tailored to each individual patient following discussion of known side-effect profiles. Treatment should aim for early and effective reduction of DME to improve best possible visual outcomes and possibly to reduce overall treatment burden. Further clinical study, including studies directly evaluating combination therapies as well as those focusing on rescue therapy, would be of special interest particularly in patients with persistent disease.
References:


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Chief Complaint

• A 58 year-old phakic woman presents for a second opinion and evaluation regarding diabetic macular edema (DME) following a period of poor follow-up.
History

• A 58 year-old phakic woman with longstanding non-proliferative diabetic retinopathy (DR) and center-involving diabetic macular edema (DME) presents for evaluation.
• Prior treatment for DME included focal laser and intravitreal injections of 1.25mg bevacizumab.
• Last treatment with bevacizumab was 10 months prior to presentation.
• The patient noted improved systemic diabetic control with a hemoglobin A1c of 7.4% on a stable diabetic medication regimen.
• Subjectively, the patient reported long-term poor visual acuity without recent sudden or significant change. She had no prior history of vitrectomy, proliferative DR, glaucoma, or prior ocular surgery.
Examination

- Motility and pupillary examination was within normal limits.
- Anterior segment: notable only for 2+ nuclear sclerotic cataract.
- No neovascularization of the iris or optic nerve.
- Optic nerve: C:D ratio 0.2, pink, symmetric.

Va $\leftarrow \frac{20}{200}$ $\frac{20}{200}$

IOP $\leftarrow 15$

16
Fundus Examination

Va < 20/200
20/200
Fluorescein angiography, OD
Fluorescein angiography, OS
Impression:

- DME OU
- Leakage noted on FA with notable intraretinal fluid and loss of outer retinal architecture on SD-OCT.
‘Real World’ Patient challenges

• Presentation at late stage of disease
• Poor visual acuity at baseline
• History of non-compliance with follow-up
• Prior history of multiple, non-standardized treatments with lack of clear documentation of relative effect
• Patient notes: difficulty with treatment visits every month; wishes for least number of treatments and least number of visits as possible
Treatment course

- Patient was treated with the following:
  - 1 additional treatment of focal laser OU
  - A series of 6, monthly injections of intravitreal 0.3mg ranibizumab
  - Patient was subsequently lost to follow-up for 2 months
  - 1 intravitreal injection of Ozurdex OD only, with resolution of DME
  - Maintenance of q3 month Ozurdex treatment interval OD
Response to treatment

• Patient was treated with the following:
  – 1 additional treatment of focal laser OU
  – A series of 6, monthly injections of intravitreal 0.3mg ranibizumab
Figure 3

Improvement in CMT OS>OD. Notes subjective improvement in vision but “still blurry” overall.
Response to treatment

• Patient was treated with the following:
  - 1 additional treatment of focal laser OU
  - A series of 6, monthly injections of intravitreal 0.3mg ranibizumab
  - Patient was subsequently lost to follow-up for 2 months
DME persists OD. Noted reduction in DME OS while not on treatment. No subjective change in vision.
Response to treatment

- Patient was treated with the following:
  - 1 additional treatment of focal laser OU
  - A series of 6, monthly injections of intravitreal 0.3mg ranibizumab
  - Patient was subsequently lost to follow-up for 2 months
  - 1 intravitreal injection of Ozurdex OD only, with resolution of DME
  - Maintenance of q3 month treatment interval OD
Resolution of DME OD. Ongoing resolution OS while not on treatment. Improved visual acuity.
Discussion

• This patient case demonstrates a common scenario encountered in ‘real world’ patients with DME:
  – periods of non-compliance with follow-up
  – history of multiple, non-standardized prior treatments
  – later presentation
  – Such patient features are not well represented in the body of prospective clinical trial data in DME patients, making a preferred management strategy for patients with persistent DME unclear.
Key points

• The case highlights several important points in regards to DME management.

• Firstly, current evidence reveals that early treatment not only results in improved visual acuity outcomes but also may reduce the number of treatments required over the long-term.
  – Phase III RISE/RIDE trials (Boyer et al)
  – Post-hoc analysis of the RISE/RISE trials (Wykoff et al)
Key points

• Secondly, evidence also notes that effective treatment for DME may be achieved with corticosteroid therapy, including at extended treatment intervals and in eyes with prior anti-VEGF treatment.
  – Intravitreal bevacizumab monotherapy versus every-three-month intravitreal Ozurdex monotherapy for persistent DME (Shah et al)
  – Sub-group analysis of the MEAD study (Augustin et al)
Our case

• In this case, the patient presented with persistent disease that was, per available records and history, never fully controlled and was treated after significant visual acuity reduction was observed.

• While subjective and objective visual acuity improvement was observed following treatment, final visual acuity was at the level of 20/100, likely owing to persistent fluid noted on OCT, underscoring the importance of early, effective treatment.

• The patient noted history of non-compliance with follow-up due to struggles with office visit frequency and perceived lack of change in visual acuity with treatment.

• Following initiation of Ozurdex, the persistent DME resolved clinically and visual acuity slightly improved. The patient reported satisfaction with subsequent every-three-month treatment intervals/monitoring.
Conclusions

- Management of a patient with persistent DME despite prior therapy is a common, yet challenging, clinical scenario.
- In this case, use of the Ozurdex implant allowed for resolution of persistent DME in a patient with variable follow-up compliance and prior incomplete response to focal laser and anti-VEGF treatment while utilizing an extended treatment interval.
- The case highlights common challenges encountered in ‘real world’ patients with DME, and underscores how treatment decisions regarding use of anti-VEGF and/or corticosteroid therapy may be used in combination and tailored to individual patient needs.
Conclusions

- With multiple treatment modalities available, including focal laser, anti-VEGF therapy, intraocular or periocular steroids, and vitrectomy, management should be tailored to each individual patient following discussion of known side-effect profiles.
- Treatment should aim for early and effective reduction of DME to improve best possible visual outcomes and possibly to reduce overall treatment burden.
- Further clinical study, including studies directly evaluating combination therapies as well as those focusing on rescue therapy, would be of special interest.
Thank you!

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