Scientific Research Publishing

Open Journal of Ophthalmology, 2024, 14, 398-404
https://www.scirp.org/journal/ojoph
ISSN Online: 2165-7416
ISSN Print: 2165-7408

Optical Coherence Tomography (OCT) Feature Identifying Niche for Dexamethasone (FIND) Intravitreal Implant in the Treatment of Anti-VEGF Slow Responders with Diabetic Macular Edema

Ram Peddada[1], Joshua C. Hollingsworth[2], David Redden[2], Eric Marin[2]

[1]Retina of Auburn & Metro-Columbus, Opelika, AL, USA
[2]VCOM, Auburn, AL, USA
Email: docrp@retinaofauburn.com

How to cite this paper: Peddada, R., Hollingsworth, J.C., Redden, D. and Marin, E. (2024) Optical Coherence Tomography (OCT) Feature Identifying Niche for Dexamethasone (FIND) Intravitreal Implant in the Treatment of Anti-VEGF Slow Responders with Diabetic Macular Edema. *Open Journal of Ophthalmology*, **14**, 398-404.
https://doi.org/10.4236/ojoph.2024.144036

Received: August 29, 2024
Accepted: November 2, 2024
Published: November 5, 2024

Abstract

This paper raises the question if intravitreal dexamethasone implant deserves to be utilized more effectively in a select subset of eyes with diabetic macular edema (DME). If so, what is the OCT morphology of such eyes? A retrospective consecutive case series is employed to answer these questions. Twenty consecutive eyes were studied: ten that have been treated with intravitreal anti-VEGF (Group A) injections and ten which have been treated with the steroidal implant (Group O) because they failed or were slow to respond to multiple injections of anti-VEGF medications. Specifically, 1) macular edema in the eyes were categorized for the type of OCT morphology and 2) their response to the respective treatments in terms of the resolution of the OCT morphology was determined. Results show that the OCT morphology of eyes that were in Group O predominantly (7/10) had the feature of posterior retinal leakage (subretinal fluid and large outer retinal cysts); this feature was rare in Group A (2/10). Further, each of these eyes (7/7) in Group O had a complete resolution of the macular edema after a single treatment with the dexamethasone intravitreal implant whereas neither eye with this feature (0/2) responded to the (anti-VEGF) treatment in Group A. This leads to the conclusion that there exists an OCT Feature that Identifies a Niche for Dexamethasone Intravitreal implant (FIND) in the treatment of anti-VEGF slow responders in DME. The clinical significance of the study is that selecting eyes with *a priori* FIND morphology on the OCT for treatment with dexamethasone implant prior to, or at the outset of, a series of anti-VEGF treatment may resolve DME promptly

and lower the treatment burden for patients and cost to society.

Keywords

Diabetic Macular Edema, Dexamethasone Intravitreal Implant, Anti-VEGF, FIND OCT Morphology

1. Background and Hypothesis

This paper addresses an important aspect of diabetic retinopathy: treatment of diabetic macular edema. In routine clinical setting, intravitreal steroidal implant, dexamethasone 0.7 mg, Ozurdex™, although FDA approved as a first line treatment for diabetic macular edema is utilized less frequently than anti-VEGF intravitreal injections. We propose that the intravitreal dexamethasone implant may be more effectively utilized with the aid of an Optical Coherence Tomography (OCT) Feature Identifying Niche for Dexamethasone (FIND) to target the inflammatory component in DME.

We hypothesize that FIND is characterized by leakage in the posterior aspect of the macula resulting in subfoveal fluid and large outer retinal cysts. We further hypothesize that this particular OCT morphology feature is common to anti-VEGF slow responders since these medications are not specifically designed to treat inflammatory changes in DME. Therefore, we suspect that such eyes will respond better to intravitreal dexamethasone implant.

2. Review of Literature

It is well known that inflammation is an important mechanism in macular edema due to diabetes and retinal vein occlusion [1] [2]. This led to a short case series [3] that showed that a specific optical coherence tomography (OCT) morphology identifies eyes with diabetic macular edema (DME) that are preferentially sensitive to triamcinolone steroid intravitreal injection relative to anti-vascular endothelial growth factor (anti-VEGF) treatment.

There have been numerous studies on the OCT morphology of DME. With advent of OCT, various morphologic features of this imaging modality were described in diabetic macular edema [4]. More recently, others [5] [6] presented additional OCT morphology characteristics in conjunction with diabetic macular edema. Although, several other studies have found OCT morphology of subfoveal fluid or serous retinal detachment is a marker for eyes that respond better to triamcinolone [7] or dexamethasone [8] intravitreal injections as opposed to anti-VEGF treated cohorts, there has not been a study reported on eyes that have either failed or were slow responders to anti-VEGF and were then treated with dexamethasone implant.

In that vein, a large cohort study [9] demonstrated that dexamethasone intravitreal implant is effective in eyes with diabetic macular edema refractory to anti-

VEGF. Others, including [10] suggested that combined steroid and anti-VEGF therapy yielded superior results to anti-VEGF monotherapy to treat DME. There was no specific discussion of OCT features that were associated with the relative success of the steroid implant in these studies. This was later confirmed by [11] who found the simultaneous double protocol therapy of dexamethasone implant and ranibizumab intravitreal injection to be an effective treatment option for DME with inflammatory biomarkers on OCT or/and decreased visual acuity.

3. Objective

We seek answers to the following two questions. As compared to anti-VEGF sensitive eyes, is there a predominant macular OCT morphology feature in the anti-VEGF slow responders? What is the success of intravitreal dexamethasone implant in treating eyes with this OCT feature?

4. Methods

We categorize OCT features as shown in Figure 1: Type 1 macular edema with subfoveal fluid and/or large central outer retinal cysts, and Type 2 with inner retinal cysts and/or mild thickening. Per our FIND hypothesis Type 1 is the OCT Feature Identifying Niche for Dexamethasone. We conducted a retrospective study of 10 consecutive eyes with DME which were treated with *any* anti-VEGF intravitreal injections in a given calendar period, Group A, and 10 consecutive eyes that were treated with Ozurdex™, Group O, in the same calendar period, after a lack of response to three or more anti-VEGF injections. To answer the first question of our objective, the OCT features of eyes from each treatment group were classified either as Type 1 or Type 2. To answer the second question, the success of intravitreal dexamethasone implant to resolve Type 1 leakage at the next follow up visit was determined. This would confirm that Type 1 is OCT Feature Identifying Niche for Dexamethasone (FIND).

Figure 1. Categorization of OCT image in diabetic macular edema (DME). (a) Type 1: with subfoveal fluid and large central outer retinal cysts and (b) Type 2: with small inner retinal cysts and thickening.

5. Results

Figure 2 shows the raw data of OCT images, pre- and post-treatment, for each eye in each group. Of the eyes with Type 1 morphology: subfoveal fluid and/or large outer retinal cysts only 2 in 10 (20%) were anti-VEGF sensitive (Group A). In contrast, this morphology was present in 7 out of 10 eyes (70%) that were resistant to anti-VEGF (slow responders) and therefore received a single-dose of intravitreal

dexamethasone implant (Group O). Table 1 shows intravitreal dexamethasone implant successfully resolved the Type 1 morphology on OCT in all 7 (100%) of these eyes at the following visit.

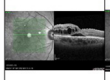
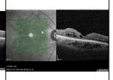
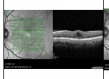
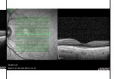
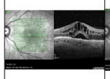
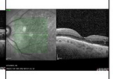
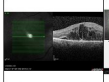
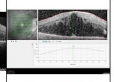
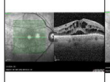
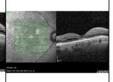
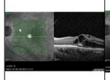
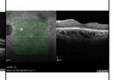
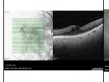
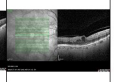
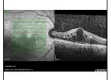
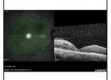
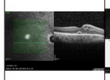
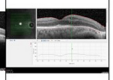
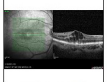
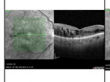
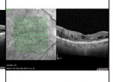
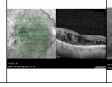
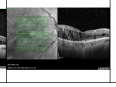
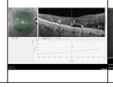
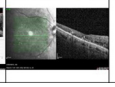
Subjects	Group	Pre	Post	Success?	Morphology	Subjects	Group	Pre	Post	Success?	Morphology
1	A			Yes (mild)	2	11	O			Yes	1
2	A			Yes	2	12	O			Yes	1
3	A			No	1	13	O			Yes	1
5	A			No	2	14	O			Yes	1
6	A			Yes (mild)	2	15	O			Yes	2
20	A			No	1	4	O			Yes	1
8	A			Yes	2	17	O			Yes	1
19	A			Yes (mild)	2	9	O			Yes (mild)	2
18	A			Yes	2	10	O			No	2
16	A			No	2	7	O			Yes	1

Figure 2. Raw data of pre- and post-treatment OCT images and categorization of OCT morphology (Type 1: with subfoveal fluid and/or large outer retinal cysts, and Type 2: without) showing success of treatment in eyes from each group (A: anti-VEGF sensitive and O: anti-VEGF slow responders, so proceeded with intravitreal dexamethasone implant (Ozurdex™) treatment).

Table 1. Frequency of type 1 in each treatment group and response to type 1 treatment.

Treatment Groups	Number of Eyes with Type 1 OCT Morphology	Success in Treating Type 1
Group A (Anti-VEGF sensitive)	2/10	0/2
Group O (Slow responders to anti-VEGF and hence transferred to Ozurdex™ implant treatment)	7/10	7/7

6. Discussion

We determined the proportion of eyes with Type 1 or Type 2 DME in 10 subjects who were anti-VEGF sensitive (*i.e.*, did not proceed to dexamethasone implant treatment; Group A) and 10 who progressed to intravitreal dexamethasone implant treatment (*i.e.*, anti-VEGF slow responders; Group O). Eyes that were resistant to anti-VEGF, and so proceeded to dexamethasone implant treatment,

were predominantly of Type 1 morphology. Further, when treated with intravitreal dexamethasone implant, all such eyes responded positively (7 out of 7). This confirmed our hypothesis that it is possible to name an OCT Feature Identifying Niche for Dexamethasone (FIND), and that is Type 1 OCT morphology. Thus, this study reports for the first time a specific OCT feature that identifies sensitivity to intravitreal dexamethasone implant treatment in eyes that were found to be not sensitive to anti-VEGF treatment in diabetic macular edema.

In terms of clinical significance, these results suggest that eyes with OCT FIND *a priori* should be treated with dexamethasone intravitreal implant at the outset of the anti-VEGF treatment. This may reduce the treatment burden of intravitreal injections in eyes potentially resistant to anti-VEGF treatment. Routinely performing a series of anti-VEGF injections and then considering intravitreal dexamethasone implant injection for slow responders may not be an effective approach.

The rationale for the success of dexamethasone intravitreal implant in eyes with subfoveal fluid and large outer retinal cysts is based on inflammation. It has been shown that eyes with serous retinal detachment (subfoveal fluid) in diabetic macular edema have elevated inflammatory marker IL-6 in the vitreous [12]. This explains why dexamethasone treatment is successful when anti-VEGF treatment is not in eyes with Type 1 diabetic macular edema or OCT FIND eyes.

This study is limited by number of eyes and the limited selection of anti-VEGF treatment in keeping with the study plan to consider consecutively treated eyes within a calendar period. Also, the number of treatments performed before concluding a lack of sensitivity to the anti-VEGF treatment (labeling as slow responders), and hence initiation of dexamethasone implant treatment was variable based on subjective and objective criteria. Further, this was a retrospective study and, although it was typically one month, the follow up time interval for each eye was variable. Similarly, more than one device was employed for the OCT scans.

Notwithstanding the above limitations, OCT FIND morphology is a predominant feature among anti-VEGF *resistant* eyes (which were hence considered for dexamethasone treatment) and, further this OCT morphology is indeed reflective of good response to dexamethasone treatment. This is a new finding with respect to dexamethasone implant that aligns with previous findings regarding triamcinolone intravitreal injections [3]. Although there were previous studies describing the OCT changes with inflammation and the benefit of dexamethasone implant in diabetic macular edema [8], this study suggests that the anti-VEGF and dexamethasone treatments occupy two different treatment spaces. This is important, because it allows for pre-selection of eyes that should be treated with steroid implant at the outset based on *a priori* OCT FIND morphology.

7. Conclusion

This study suggests that steroid sensitive OCT morphology, FIND, provides a tool to create a niche for dexamethasone intravitreal implant to treat diabetic macular

edema at the outset. Employing this concept may help resolve diabetic macular edema sooner in select eyes, thus lowering the treatment burden for patients and cost to society.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Funatsu, H., Noma, H., Mimura, T., Eguchi, S. and Hori, S. (2009) Association of Vitreous Inflammatory Factors with Diabetic Macular Edema. *Ophthalmology*, **116**, 73-79. https://doi.org/10.1016/j.ophtha.2008.09.037

[2] Noma, H., Mimura, T., Yasuda, K. and Shimura, M. (2014) Role of Inflammation in Diabetic Macular Edema. *Ophthalmologica*, **232**, 127-135. https://doi.org/10.1159/000364955

[3] Peddada, R. (2014) Subfoveal Fluid Is a Sign of Kenalog Sensitive Retinal Leakage. *Proceedings of XI Congress of Southeastern European Society of Ophthalmology*, Bucharest, 4 October 2014, 49.

[4] Otani, T., Kishi, S. and Maruyama, Y. (1999) Patterns of Diabetic Macular Edema with Optical Coherence Tomography. *American Journal of Ophthalmology*, **127**, 688-693. https://doi.org/10.1016/s0002-9394(99)00033-1

[5] Chung, Y., Kim, Y.H., Ha, S.J., Byeon, H., Cho, C., Kim, J.H., *et al.* (2019) Role of Inflammation in Classification of Diabetic Macular Edema by Optical Coherence Tomography. *Journal of Diabetes Research*, **2019**, Article ID: 8164250. https://doi.org/10.1155/2019/8164250

[6] Zhou, J., Song, S., Zhang, Y., Jin, K. and Ye, J. (2022) Oct-Based Biomarkers Are Associated with Systemic Inflammation in Patients with Treatment-Naïve Diabetic Macular Edema. *Ophthalmology and Therapy*, **11**, 2153-2167. https://doi.org/10.1007/s40123-022-00576-x

[7] Liu, Q., Hu, Y., Yu, H., Yuan, L., Hu, J., Atik, A., *et al.* (2015) Comparison of Intravitreal Triamcinolone Acetonide versus Intravitreal Bevacizumab as the Primary Treatment of Clinically Significant Macular Edema. *Retina*, **35**, 272-279. https://doi.org/10.1097/iae.0000000000000300

[8] Zur, D., Iglicki, M., Busch, C., Invernizzi, A., Mariussi, M., Loewenstein, A., *et al.* (2018) OCT Biomarkers as Functional Outcome Predictors in Diabetic Macular Edema Treated with Dexamethasone Implant. *Ophthalmology*, **125**, 267-275. https://doi.org/10.1016/j.ophtha.2017.08.031

[9] Mitchell, P., Arnold, J., Fraser-Bell, S., Kang, H.K., Chang, A.A., Tainton, J., *et al.* (2023) Dexamethasone Intravitreal Implant in Diabetic Macular Oedema Refractory to Anti-Vascular Endothelial Growth Factors: The AUSSIEDEX Study. *BMJ Open Ophthalmology*, **8**, e001224. https://doi.org/10.1136/bmjophth-2022-001224

[10] Osman Saatci, A., Ayhan, Z. and Durmaz Engin, C. (2016) Simultaneous Intravitreal Ranibizumab and Dexamethasone Implant Administration at the Same Setting in Eyes with Severe Diabetic Macular Edema. *Open Journal of Ophthalmology*, **6**, 112-118. https://doi.org/10.4236/ojoph.2016.62016

[11] Kaya, M., Atas, F., Kocak, N., Ozturk, T., Ayhan, Z. and Kaynak, S. (2023) Intravitreal Ranibizumab and Dexamethasone Implant Injections as Primary Treatment of Diabetic Macular Edema: The Month 24 Results from Simultaneously Double Protocol. *Current Eye Research*, **48**, 498-505. https://doi.org/10.1080/02713683.2023.2168013

[12] Sonoda, S., Sakamoto, T., Yamashita, T., Shirasawa, M., Otsuka, H. and Sonoda, Y. (2014) Retinal Morphologic Changes and Concentrations of Cytokines in Eyes with Diabetic Macular Edema. *Retina*, **34**, 741-748. https://doi.org/10.1097/iae.0b013e3182a48917