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# Anti-VEGF crunch syndrome in proliferative diabetic retinopathy after aflibercept intravitreal injection

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***ABSTRACT**: Purpose: To assess the short-term complications of a single dose of intravitreal aflibercept in patients with proliferative diabetic retinopathy (PDR).*
*Methods: retrospective review of 32 patients who where treated with intravitreal injection of aflibercept (40mg/mL)*
*Results: One patient out of 32 presented with tractional retinal detachment 8 days after intravitreal injection of aflibercept in his left eye. This case underwent pars plana vitrectomy, removal of all epiretinal fibrivascular membranes, endolaserpanretinal photocoagulation and silicone tamponade in the same eye.*
*Conclusion: Tractional retinal detachment may occur in a short time post intravitreal injection of aflibercept in patients with proliferative diabetic retinopathy.*
***KEYWORDS:** crunch syndrome, aflibercept, PDR*

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## I. INTRODUCTION

Proliferative diabetic retinopathy (PDR) is a severe complication of diabetes. It is a leading cause of blindness, affecting approximately 7% of patients with diabetes mellitus (1). PDR hallmarks are retinal neovascularisation, fibrovascular proliferation, and retinal capillary leakage which leads to vitreous haemorrhage (VH) and tractional retinal detachment (TRD) (17,18). Standard of treatment of PDR for forty years has been panretinal photocoagulation (PRP) (2), but in recent years intravitreal anti-vascular endothelial growth factor ( anti-VEGF) has proven to be effective for complete or partial regression of neovascularization (3). There are three main anti-VEGF drug for ophthalmic intravitreal injection: aflibercept (Eyelea$^{TM}$), bevacizumab (Avastin) and ranibizumab (Lucentis$^{TM}$). Only aflibercept and ranibizumab have received marketing authorisation for the treatment of DMO.

Aflibercept (Eyelea$^{TM}$), is a soluble decoy receptor that binds vascular endothelial growth factor-A (VEGF-A), VEGF-B and placental growth factor (PIGF)(8) with a greater affinity than the body's native receptors. It is a decoy receptor as VEGF does not bind to its original receptors but mistakenly binds with aflibercept, thereby reducing VEGF's activity. VEGF-A is a biochemical signal protein that promotes angiogenesis throughout the body and in the eye. By decreasing VEGF-A's activation of its native receptors, aflibercept reduces subsequent growth of new blood vessels. (9)

In spite of the efficacy of anti-VEGF this treatment is reported to have some serious adverse effects including progression or development of TRD , known as 'crunch syndrome' (4,5,6,7,) TRD represents the separation of the neurosensory retina from the underlying retinal pigment epithelium due to the traction forces from membranes in the vitreous or over the retinal surface. This phenomenon as a complication following intravitreal injection of anti- VEGF has been described as 'crunch syndrome', 'crunch effect' and 'crunch phenomenon'. Although there is no agreed-upon definition in the literature, crunch syndrome is well documented in patients after treatment with bevacizumab (10,11) and ranibizumab (12). However, currently there is no publication linking intravitreal aflibercept with anti-VEGF crunch for the treatment of PDR. In this article we report the outcomes of a retrospective study of 32 patients with PDR who were injected with aflibercept (Eyelea$^{TM}$40mg/ mL) intravitreally as a primary treatment. Out of all the cohort only one patient has developed a 'crunch syndrome' in the treated eye 8 days after injection.

## II. Case report

A74-year old man R.R. with Type 2 diebetes mellitus, visual acuity in the initial visit was 0.15 in the right eye and 0.05 in the left eye. Fundus examination revealed PDR in both eyes with PRP in the right eye and

vitreous haemorrhage and ring shaped fibrovascular membrane in the left eye. Fluorescein angiography revealed marked hyper fluorescence secondary to neovascularisation. We injected intravitreal aflibercept ( 40mg/mL) in the left eye. Eight days later the patient was referred from a local ophthalmologist to the ER with TRD in the left eye with visual acuity PPLC. The traction was confirmed by ultrasonography. Vitrectomy was performed with good anatomic result, the visual acuity was 0.01.

## III. Discussion

The exact mechanism of anti-VEGF crunch is unclear. PDR is characterized by angiogenesis due to VEGF upregulation, vascular growth , fibrous tissue formation and eventual contraction of fibrous tissue that results in TRD (4). Even though reports have considered the possibility of anti-VEGF crunch as a natural progression of PDR (13, 7), the short interval between injection and crunch onset suggest a cause and effect relationship. A theory that could explain this phenomenon is the 'angiofibrotic switch'. It is defined as the balance between VEGF and connective tissue growth factor (CTGF) and is a strong predictor of the degree of fibrosis that predisposes to contraction (14, 15). CTGF is a profibrogenic protein that is found in wound healing elevated levels as well as in the vitreous fluid of PDR patients (15). After the injection of anti-VEGF agent the concentration of VEGF is reduced in contrast to the CTFG concentration which remain constant. Kupier and coworkers proposed that the imbalance between CTGF and VEGF may create a profibrotic environment that stimulated fibrosis and increases the risk of TRD.

In a literature review of 3 reports of crunch syndrome after anti-VEGF injection the percentage of crunch syndrome as a complication varied between 1.5% and 5.3% (16). However none of this reviews have used aflibercept. In our study 1 out of 32 patients with PDR ( 3.1%) has developed anti-VEGF crunch syndrome.

**Table 1** Reported incidence of anti-VEGF crunch syndrome in PDR patients

| Study (year) | Design | Study population | Intervention | No of patients | Cases of crunch |
|---|---|---|---|---|---|
| Sergeeva( 2021) | Retrospective single arm | PDR, no prior treatment | Aflibercept | 32 | 1 (3.1%) |
| Moradian( 2008 ) | Retrospective single arm | Progressive PDR | Bevacizumab | 38 | 2 (5.3%) |
| Torres- Soriano ( 2009 ) | Retrospective single arm | PDR | Bevacizumab | 343 | 5 (1.5%) |
| Arevalo ( 2008 ) | Retrospective single arm | PDR refractory to PRP | Bevacizumab | 698 | 25 (3.6%) |

## IV. Conclusion

Anti- VEGF crunch syndrome will continue to be an important and difficult topic for medical and surgical ophthalmologists. It is a serious adverse event associated with anti-VEGF treatment of PDR patients. The results of this study do not show big difference compared to the studies with bevacizumab. However the study population was limited to 32 patients and no standardized data other than ultrasonography and visual acuity was used to compare results between reviews. Therefore more studies with standardized criteria should be performed, especially ones investigating the rate of TDR complications after aflibercept in PDR patients. In conclusion we recommend close monitoring of patients undergoing aflibercept (40mg/mL) intravitreal injection and well timed surgical treatment when needed.

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