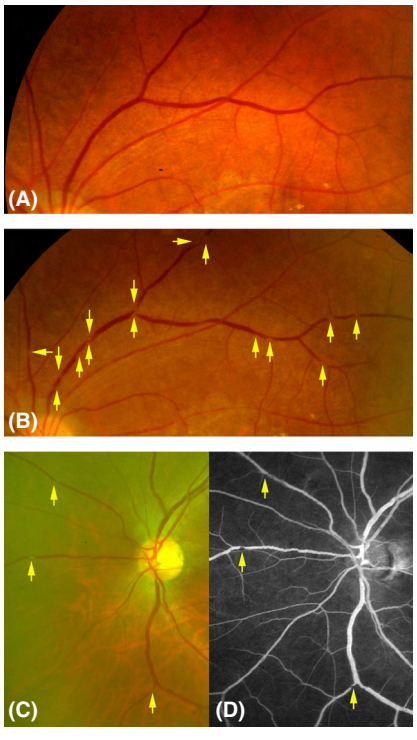

Fig. 1. Multiple retinal vein thromboses. (A) A fundus photograph of the left eye from case 1 before treatment. (B) A fundus photograph of the left eye from case 1 shows multiple retinal vein thromboses following intravitreal aflibercept injections. The arrows indicate retinal vein thrombi. (C) A fundus photograph of the left eye from case 4 shows multiple retinal vein thromboses. The arrows indicate retinal vein thrombi. (D) A fluorescein angiogram of the left eye from case 4 shows venous stenosis at the sites of the thrombi. The arrows indicate venous stenosis.

thromboembolic events (Van Cutsem et al. 2012). Therefore, it seems reasonable to assume that the multiple retinal vein thromboses observed in the current case series were attributable to the IAIs.

In the current case series, multiple retinal vein thromboses were observed only in patients treated with IAIs but not with IRIs. Possible explanations are that aflibercept has a higher affinity for VEGF-A and an ability to bind VEGF-B and placental growth factor compared with ranibizumab (Papadopoulos et al. 2012). Another possible explanation is that aflibercept has an Fc region. *In vitro* experiments have shown that aflibercept, but not ranibizumab, forms immune complexes with VEGF-B and activates platelets via FcγRIIa (Nomura et al. 2015).

The limitations of the current study were that it was retrospective in nature and limited to four cases. The exact pathogenesis of multiple retinal vein thromboses remains unclear, and a definite causal relationship between multiple retinal vein thromboses and IAIs has not been established. Further studies with a larger sample size are necessary to confirm the effect of multiple retinal vein thromboses on visual function and the systemic circulation.

Although rare, multiple retinal vein thromboses may occur in patients with age-related macular degeneration treated with IAIs. Treatment regimens, including selection of anti-VEGF agents and injection frequency, should be reconsidered in cases of occurrence.

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Treatment algorithm with dexamethasone intravitreal implant in patients with diabetic macular edema

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Editor,

Anti-VEGF (vascular endothelial growth factor) treatment for wet age-related macular degeneration (AMD) and diabetic macular edema (DME) is well established. Since it requires many clinical visits and frequent injections, different treatment regimens have been discussed, from monthly treatment to pro re nata (treatment when needed) and treat and extend (T&E), a proactive treatment regimen where injection is given at every follow-up visit with extended intervals. In the treatment of wet AMD, T&E regimen has been shown to be superior to other regimens with a better visual outcome despite fewer injections (Augsburger et al. 2019).

Ozurdex (dexamethasone 0.7 mg implant) is also available for the treatment of DME and has shown comparable results with anti-VEGF in both gain of Visual Acuity (VA) and reduction of retinal thickness (Boyer et al. 2014). The possible side-effects of intravitreal dexamethasone implant, that is cataract development and increased intraocular pressure (IOP), have made it a second-choice drug in

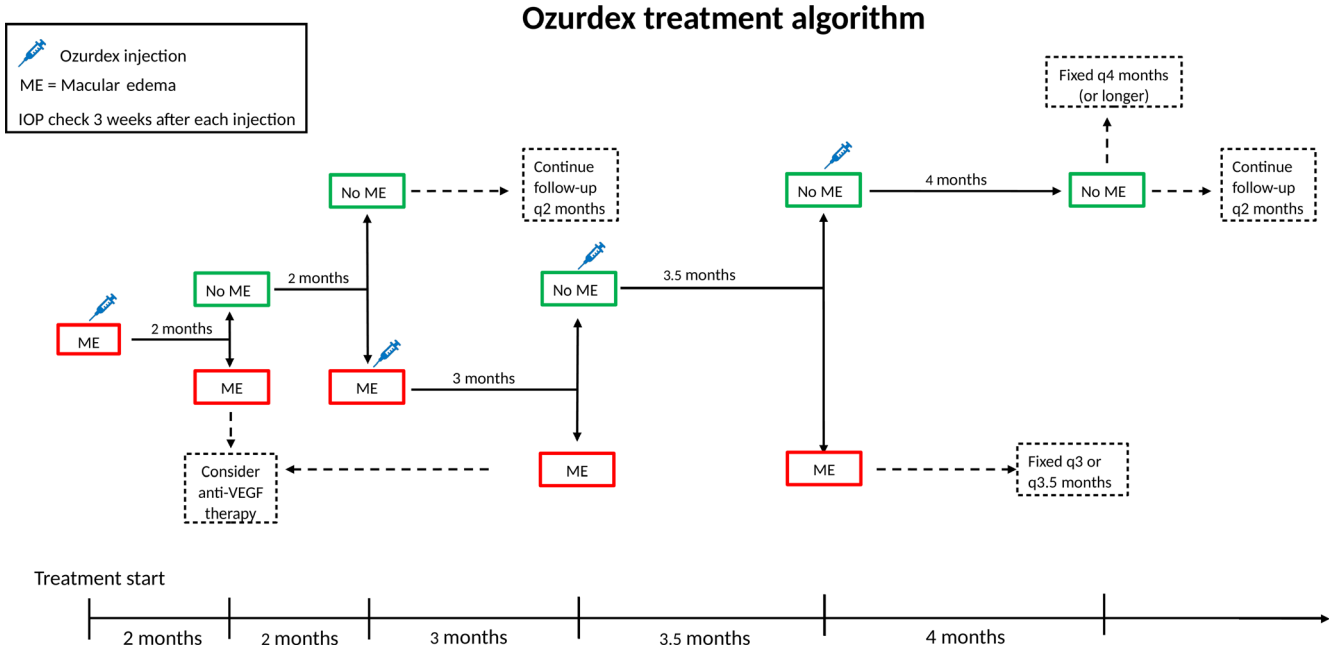

Fig. 1. First follow-up after the injection; month 2. Good responder; next visit month 4; No responder; stop treatment. Recurrence of edema at month 4; reinjection. Next visit; month 3; No recurrence month 4; observation with fixed intervals. Edema at month 4 but no edema at month 3, reinjection on a dry retina. Next visit; 3.5 months. If incipient edema at month 3.5, the patient is scheduled for treatment with fixed intervals between 3 and 3.5 months. No edema at month 3.5; next interval can be extended to 4 months.

the treatment of DME. The European guidelines (Schmidt-Erfurth et al. 2017) recommended the use of Ozurdex in patients not responding to three to six anti-VEGF injections. However, Ozurdex could be considered as first-line treatment in pseudophakic eyes, in patients with anamnesis of a recent major vascular event and in cases with expected poor compliance.

In the clinical trials (Boyer et al. 2014), Ozurdex was administered every 6 months. However, most real-world data report a maintained effect around 4 months. In clinical practice, the treatment regimen used with Ozurdex is pro re nata. The patient receives an Ozurdex injection, within 1 month IOP is measured, and after 2 months the effect is assessed. The next follow-up visit is scheduled after another 2 months, that is at month 4 after the injection. If recurrence of edema is detected, the patient is reinjected; otherwise, a new appointment is set after another 2 months. With this approach, the patient is treated only when a recurrence of edema is seen. This may jeopardize retinal structure and function and result in a poor visual outcome over time.

In a recent Spanish study, a proactive treatment protocol, describing the time-point for follow-up visits and retreatments, has been illustrated (García-Layana et al. 2018). In a Swedish study group, we have developed a treatment algorithm for dexamethasone, with intent to optimize the number of injections, follow-up visits and treatment outcome (Fig. 1). The intention is that this algorithm would work as a useful tool for clinicians to optimize and facilitate the treatment with Ozurdex, once the decision for initiating the treatment has been made.

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[Correction added on 25 February 2020 after first publication: the conflict of interest has been included in this version.]