Treatment of Proliferative Diabetic Retinopathy with Intravitreous Injection of Ranibizumab

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ABSTRACT

The current treatment for proliferative diabetic retinopathy (PDR), panretinal photocoagulation (PRP), has many side effects. PDR develops because of vascular endothelial growth factor (VEGF) production from the retina, but there are limited descriptions of the use of anti-VEGF therapy, specifically ranibizumab, for PDR. We report the treatment of PDR with intravitreous injections of ranibizumab, with more than one year of follow-up.

A 20 year-old patient with diabetes mellitus was found to have PDR in each eye after presenting with decreased visual acuity. He refused to receive PRP due to fear of pain and loss of peripheral and night vision. Instead, after informed consent, he received three intravitreous anti-VEGF injections with ranibizumab (Lucentis®, Genentech, South San Francisco) in each eye, spaced out over several months. He had regression of neovascularization within two to four weeks of the initial treatments, and he maintained excellent visual acuity with no evidence of recurrent neovascularization through 17 months after initiating treatment.

Intravitreous injections of anti-VEGF therapy may be an alternative treatment option for patients with PDR. Furthermore, the maintenance of regression of PDR following anti-VEGF therapy may persist without the need to continue monthly injections long-term.

INTRODUCTION

Diabetic retinopathy is the leading cause of irreversible visual loss and new-onset blindness in the United States among adults aged 20-74 years.¹ It is a common complication of diabetes caused by production of vascular endothelial growth factor (VEGF) in the eyes of some patients with elevated blood sugars. The early stage of diabetic retinopathy is non-proliferative diabetic retinopathy, which is characterized by retinal vascular abnormalities such as microaneurysms, intraretinal hemorrhages, nerve fiber layer infarcts, intraretinal microvascular abnormalities, and venous beading.² Over time, retinal capillary closure can occur, and parts of the retina may become ischemic or infarcted. VEGF...
released by the ischemic retina can stimulate the growth of abnormal capillaries, termed neovascularization at the disc or elsewhere in the retina, which are features of proliferative diabetic retinopathy (PDR). VEGF also can cause hyper-permeability of retinal vessels, which can lead to vision loss from diabetic macular edema (DME), i.e., swelling or thickening of the center of the retina. It is estimated that 1 of every 12 persons with diabetes mellitus over 40 years of age has advanced, vision-threatening retinopathy, including PDR or DME. With aging of the United States population and the increasing age-specific prevalence of diabetes, diabetic retinopathy, including PDR, is an important public health priority.

Currently, panretinal photocoagulation (PRP), which destroys part of the ischemic retina, thus reducing the release of VEGF, is the standard treatment for PDR. Close to 60% of patients show regression of neovascularization within 3 months of PRP treatment. However, there are many adverse effects of PRP, including pain, decreased peripheral and night vision, increased risk of macular edema, and progression of visual loss in nearly five percent of patients despite treatment. Decreased peripheral and night vision are unavoidable side effects to this inherently destructive procedure. Thus, many efforts to look into alternative therapeutic strategies for PDR exist, with promising results from anti-VEGF agents such as pegaptanib and bevacizumab. However, few studies have reported the effects of ranibizumab, an anti-VEGF agent known to be highly effective in the treatment of ocular neovascularization associated with age-related macular degeneration, in PDR. There are no previous studies, to our knowledge, that report use of ranibizumab, without concurrent use of PRP or vitrectomy, for PDR in the absence of vitreous hemorrhage or diabetic macular edema, with follow-up of more than one year. We report such a case in a young man with proliferative diabetic retinopathy.

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**CASE PRESENTATION**

A 20-year-old man with a history of uncontrolled Type 1 diabetes, with hemoglobin A1c values as high as 12 or 13, was referred to a retina specialist for management of diabetic eye disease. On initial presentation, visual acuity was 20/40 in both eyes. Clinical examination and fundus photographs revealed severe non-proliferative diabetic retinopathy in both eyes and some questionable retinal neovascularization along the superotemporal arcade in the left eye (Figure 1). Three months later, he returned complaining of intermittent blind spots in his vision, and his visual acuity worsened to 20/50 in the right eye and 20/63 in the left eye. Clinical examination and fundus photographs revealed that he had developed PDR in both eyes, characterized by neovascularization of the discs, accompanied by an increase in intraretinal hemorrhages and microaneurysms throughout the posterior pole of the retina (Figure 2). A recommendation to begin PRP was made, although the patient was reluctant to receive this treatment due to fear of pain and loss of peripheral and night vision, and thus was told to return within a month while he seriously considered this thera-

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**Figure 1**. Initial presentation. Fundus photographs of the right (A) and left (B) eyes showing multiple microaneurysms (closed arrows), nerve fiber layer infarcts (curved arrows), and questionable retinal neovascularization elsewhere along the superotemporal arcade in the left eye (open arrow).
py. When the patient continued to refuse PRP one month later, he was offered an alternative treatment of intravitreous anti-VEGF therapy with ranibizumab, as studies had suggested that use of anti-VEGF therapy for DME also caused regression of PDR. The patient consented to receive ranibizumab injection in the right eye at this visit and signed a written informed consent form that documented this consent. A month after the injection, visual acuity in the right eye improved from 20/50 to 20/25, while fundus photographs revealed a marked decrease in the extent of intraretinal microvascular abnormalities and neovascularization in the right eye (Figure 3B). The right eye received two more injections of ranibizumab, spaced one month apart from the first injection and from each other, with continued resolution of much of his neovascularization in the right eye. Seven-one weeks following the first ranibizumab treatment in the right eye (61 weeks after the last ranibizumab treatment), the right eye had a visual acuity of 20/20, and it continued to show resolution of neovascularization and no macular edema (Figure 3C).

Due to the substantial improvement following ranibizumab treatment in the right eye, the patient requested to proceed with ranibizumab injection in the left eye one month following initiation of ranibizumab treatment in the right eye (Figure 4A). Two weeks following the left eye injection, the left eye also demonstrated decreased neovascularization of the disc and retina, although there was increased pre-retinal hemorrhage in the left eye, presumably associated with contraction of the new vessels as the neovascularization regressed (Figure 4B). Visual acuity of the left eye improved from 20/63 to 20/40 at this visit. The left eye received two additional injections of ranibizumab, one given one month after the first treatment, and the last given three months after the second treatment. The pre-retinal hemorrhage in the left eye gradually cleared over a period of nine months, while evidence of the regression of neovascularization persisted from two weeks after the first injection (Figure 4B) to the end of the follow-up period 67 weeks after the first treatment in the left eye (47

**Figure 2.** Development of proliferative diabetic retinopathy. Fundus photographs of the right (A) and left (B) eyes showing neovascularization of the discs (open arrows), as well as multiple microaneurysms and dot and blot intraretinal hemorrhages (closed arrows), and increased number of nerve fiber layer infarcts (curved arrows).

**Figure 3.** Response of right eye to ranibizumab. Fundus photographs of the right eye before (A), 4 weeks following (B), and 71 weeks following (C) the initial ranibizumab injection. Neovascularization of the disc and many of the dot and blot hemorrhages have largely regressed in (B), and (C) shows further resolution of the hemorrhages and nerve fiber layer infarcts.

**Figure 4.** Response of left eye to ranibizumab. Fundus photographs of the left eye showing neovascularization at the disc (closed arrows) before (A), obscured by pre-retinal hemorrhage (open arrows) 2 weeks following (B), and with no evidence at 67 weeks following (C) the initial ranibizumab injection. In (B), dot and blot intraretinal hemorrhages have largely regressed. In (C), most retinal vascular abnormalities have resolved.
weeks after the last treatment in the left eye; Figure 4C). The visual acuity of the left eye had improved to 20/20 at the last follow-up visit.

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**DISCUSSION**

Previous studies have suggested that intravitreal injection of anti-VEGF agents, such as pegaptanib or bevacizumab, might be a promising treatment modality for PDR. However, these reports have had relatively short follow-up periods, with only one report having up to 52 weeks after the initial treatment. Additionally, few studies have been published on the effects of ranibizumab in PDR in the absence of diabetic macular edema or vitreous hemorrhage. Ranibizumab is an anti-VEGF agent known to be effective in the treatment of ocular neovascularization associated with age-related macular degeneration, has been proven to be superior to macular laser for treating diabetic macular edema, and has the potential to be effective in other neovascular processes of the eye such as PDR. In both patients with and without PDR, there is currently stronger evidence in peer-reviewed literature supporting the use of ranibizumab to avoid worsening and to increase the chance of improvement of the diabetic retinopathy severity level than there is for pegaptanib or bevacizumab. Specifically, the Diabetic Retinopathy Clinical Research Network (DRCR.net), sponsored by the National Eye Institute, and subsequently RIDE and RISE trials sponsored by the manufacturers of ranibizumab and bevacizumab, published secondary outcome evidence from randomized clinical trials showing that ranibizumab compared with no ranibizumab increased the chance of improvement and decreased the chance of worsening in the diabetic retinopathy severity level. Other anti-VEGF drugs such as pegaptanib and bevacizumab only have evidence from case series and smaller trials. Ranibizumab injections have been shown to be safe in treating patients both with and without diabetes. The most common side effects are slight eye pain or discomfort, conjunctival hemorrhage, and intraocular pressure increase, all of which are transient and usually well tolerated. To our knowledge, prior to this report, no study has been published on the beneficial effects of ranibizumab, used alone and not in combination with PRP or vitrectomy, on PDR in the absence of vitreous hemorrhage or diabetic macular edema, with more than a year of follow-up. This case demonstrates the use of intravitreal injections of ranibizumab in the treatment of PDR in the absence of PRP, with regression of neovascularization evident within 2 to 4 weeks of the initial injection, and with persistent resolution of neovascularization for at least 71 weeks after the initial treatment. In addition, the case suggests that the beneficial effects of ranibizumab may be persistent without the need for long-term recurrent injections, even though the agent clears the vitreous cavity by about a month after injection. This long-term effect is suggested by the fact that the neovascularization did not recur 61 weeks and 47 weeks after the last treatment in the right and left eyes of this patient, respectively. The case also suggests that ranibizumab may be an alternative treatment option for patients who either refuse PRP or cannot receive it due to extensive vitreous hemorrhage (in the absence of traction retinal detachment requiring vitrectomy). Nevertheless, more comprehensive studies are needed to determine more definitively the role of intravitreal injections of anti-VEGF agents in the treatment of PDR. The National Eye Institute-sponsored Diabetic Retinopathy Clinical Research Network (DRCR.net) is currently conducting a multi-center randomized clinical trial comparing prompt PRP versus ranibizumab with deferred PRP. The results of this study, and others like it, should help determine treatment options to be considered for a patient with PDR.
LEARNING POINTS

- Diabetic retinopathy is the leading cause of visual loss and new-onset blindness among working-aged adults in the United States, and proliferative diabetic retinopathy (PDR) is one of its most visually disabling complications.

- Current standard care for PDR is panretinal photocoagulation (PRP), but it has many adverse effects including pain, decreased peripheral and night vision, increased risk of macular edema, and progression of visual loss in nearly 5 percent of patients despite treatment.

- Intravitreous injections of anti-VEGF agents such as ranibizumab may be an alternative treatment option for patients with PDR, with the potential to maintain its beneficial effects without needing chronic recurrent injections.

REFERENCES


