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# Bevacizumab therapy in patients with active proliferative diabetic retinopathy after panretinal laser photocoagulation

## Zdravljenje z bevacizumabom pri bolnikih z aktivno proliferativno diabetično retinopatijo po panretinalni laserski fotokoagulaciji

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## Abstract

**Purpose:** Evaluation of the results of treatment with bevacizumab in a group of patients with still active proliferative diabetic retinopathy (PDR) despite previous intensive laser treatment.

**Methods:** Retrospective data review of patients managed in one of the anti-VEGF therapy clinics at the University Eye Hospital in the period from May 2011 to May 2019. Patients treated with bevacizumab due to active PDR with vitreous haemorrhage after panretinal laser photocoagulation were included. Patients with active PDR and diabetic macular oedema (DME) or any other eye disease were excluded. Age and gender of patients, type of diabetes, previous ocular treatment, visual acuity at the beginning of treatment with bevacizumab, presence of iris neovascularization, number of injections received, follow-up period, visual acuity at the last follow-up examination and possible complications were all noted.

**Results:** Eleven patients with active PDR and recidivant vitreous haemorrhage were treated with bevacizumab. All patients had been treated by panretinal laser photocoagulation previously; one patient also had vitrectomy. Average best corrected visual acuity at the beginning of treatment was 57.2 ± 25.9 ETDRS letters and at the follow-up examination 6–8 weeks after the last injection, it was 64.5 ± 16.7 ETDRS letters. Patients were followed from 1 to 8 years. An average number of injections per patient per year was 2.1 ± 1.1. Four patients remained stable after discontinuing the injections; in the remaining 7 patients, vitreous haemorrhage recurred. There was no progression of PDR and there were no complications of treatment during follow-up period.

**Conclusion:** Regression of neovascularization was achieved with the use of bevacizumab in our patients and progression of PDR was prevented. Anti-VEGF therapy can be an effective option to prevent the progression of PDR in patients in whom other treatment modalities are not sufficiently effective or feasible.

## Izvleček

**Namen:** Oceniti rezultate zdravljenja z zaviralcem rastnega dejavnika za endotelij žil bevacizumabom pri bolnikih s proliferativno diabetično retinopatijo (PDR), pri katerih je bolezen še aktivna kljub intenzivnemu predhodnemu laserskemu zdravljenju.

**Metode:** Retrospektivni pregled dokumentacije bolnikov, ki so bili zdravljeni v eni od ambulant za anti-VEGF (zdravljenje z zaviralci rastnega dejavnika za endotelij žil) zdravljenje Očesne klinike od maja 2011 do maja 2019. Vključili smo bolnike, ki so bili zdravljeni z bevacizumabom zaradi aktivne PDR s krvavitvijo v steklovino in so že opravili panretinalno lasersko fotokoagulacijo. Bol-

nikov z aktivno PDR, ki so imeli diabetični makularni edem (DME) ali druge očesne bolezni, nismo vključili. Zabeležili smo starost, spol, tip sladkorne bolezni, predhodno zdravljenje, vidno ostrino ob začetku zdravljenja z bevacizumabom, morebitno prisotnost neovaskularizacij na šarenici, število prejetih injekcij bevacizumaba, trajanje spremljanja bolnikov, vidno ostrino ob zadnji kontroli. Preverili smo tudi morebiten nastanek zapletov zdravljenja.

**Rezultati:** Z bevacizumabom je bilo zdravljenih 11 bolnikov z aktivno PDR s ponavljajočimi se krvavitvami v steklovino. Vsem smo že opravili obsežno panretinalno lasersko fotokoagulacijo, enemu tudi vitrektomijo. Povprečna najboljša korigirana vidna ostrina ob začetku zdravljenja je bila 57,2 ± 25,9 črk ETDRS, ob kontroli 6–8 tednov po zadnji injekciji bevacizumaba pa 64,5 ± 16,7 črk ETDRS. Bolnike smo spremljali od 1 do 8 let. Povprečno število injekcij na enega bolnika na leto zdravljenja je bilo 2,1 ± 1,1. Pri 4 bolnikih v času spremljanja ni prišlo do ponovnega poslabšanja po prekinitvi zdravljenja, pri ostalih 7 bolnikih pa so se krvavitve ponovile. V času spremljanja pri nobenem od bolnikov nismo beležili napredovanja PDR ali zapletov zdravljenja.

**Zaključek:** Z uporabo bevacizumaba smo pri naših bolnikih dosegli regresijo neovaskularizacij in preprečili napredovanje PDR. Anti-VEGF zdravljenje je lahko učinkovito za preprečevanje napredovanja PDR pri bolnikih, pri katerih drugi načini zdravljenja niso dovolj učinkoviti ali niso izvedljivi.

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## 1 Introduction

Proliferative diabetic retinopathy (PDR) is a progressive form of diabetic retinopathy, characterized by the presence of neovascularisations. Complications of neovascularization are vitreous haemorrhages or tractional retinal detachment. Both can seriously impair vision. Approximately 7% of patients with diabetes have PDR (1). In about half of patients with PDR, vision gets severely impaired if left untreated (2).

Until recently, panretinal laser photocoagulation was the first and only choice for the treatment of PDR. The results of the DRS (Diabetic Retinopathy Study) study showed that patients with high-risk PDR, who had already undergone panretinal laser photocoagulation, had a reduced risk of severe vision loss by more than 50% (2). If there are fewer neovascularisations in the first three months after panretinal laser photocoagulation, the outcome of treatment is generally good in terms of vision.

Laser photocoagulation thermally damages the ischemic retina, thereby reducing the ischemic stimulus for angiogenesis and thus the proliferation of neovascularisations. With a timely and sufficiently extensive panretinal laser photocoagulation, we can achieve regression of neovascularisations, thereby reducing the possibility of complications such as vitreous haemorrhage and tractional retinal detachment. Despite proven positive effects, panretinal laser photocoagulation does have some side effects and complications such as loss of peripheral vision, nyctalopia, exacerbation of macular oedema, uveal effusion, vitreous haemorrhage. The procedure can be quite painful for some patients (3). Panretinal laser photocoag-

ulation cannot be performed on patients who do not cooperate and/or have cloudy optical media, e.g., dense cataract or vitreous haemorrhage.

If vitreous haemorrhage shows no signs of resorption, a vitrectomy is required; namely, in patients with type 1 diabetes within 3 months of the onset of haemorrhage, and in patients with type 2 diabetes within 6 months of the onset of haemorrhage (4). If vitrectomy is not performed in the first months after the onset of haemorrhage, proliferative change progression and the development of tractional retinal detachment are more likely, especially in patients with type 1 (5) diabetes. After vitrectomy, haemorrhage recurs or persists in 13–40% of patients. These are haemorrhages from residual or newly formed neovascularisations (6). The success of vitrectomy also depends on systemic – and not merely ocular – factors.

Vascular endothelial growth factor (VEGF) plays a key role in the development of PDR. VEGF levels are highly elevated in the retina and vitreous in patients with diabetic retinopathy (7). Studies examining the efficacy and safety of anti-vascular endothelial growth factor (anti-VEGF) medications for the treatment of diabetic macular oedema (DME) have shown that in patients, treated with anti-vascular oedema VEGF medications due to DME, the degree of diabetic retinopathy has also improved, or rather, that a regression of diabetic retinopathy occurred (8,9).

Anti-VEGF drugs can be used in everyday clinical practice as adjunctive therapies for patients with whom, even after panretinal laser photocoagulation, adequate regression of neovascularisations does not occur. (10). If panretinal laser photocoagulation is not possible in patients with PDR and vitreous haemorrhage, anti-VEGF medications may also be used, mostly prior to the planned vitrectomy (11). Occasionally, anti-VEGF drugs are chosen for a patient who refuses vitrectomy, or when the latter is not feasible for other medical reasons, or for a patient who experienced recurrent haemorrhaging following a vitrectomy.

Our aim is to evaluate the results of treatment with the bevacizumab anti-VEGF medication in a group of patients who are still experiencing active PDR despite previous intensive laser treatment.

## 2 Methods

We retrospectively reviewed the documentation of patients treated in one of the outpatient clinics for anti-VEGF treatment from May 2011 to May 2019. 11 patients were treated for active PDR, which resulted in recurrent vitreous haemorrhages despite priorly performed panretinal photocoagulation; in one case, also despite a previously performed vitrectomy. Patients with active PDR who had DME or other eye diseases were not included.

All patients were carefully ophthalmologically examined at each follow-up examination. Anterior and posterior biomicroscopy were performed to determine the best-corrected visual acuity using the ETDRS chart. A standardized chart was introduced in the ETDRS study (i.e., Early Treatment Diabetic Retinopathy Study). It allows for a more accurate determination of visual acuity than a normal Snellen chart, as visual acuity is expressed as the number of all letters read. Patients had their intraocular pressure measured and imaging with optical coherence tomography (OCT) was performed to assess the thickness and structure of the retina in the macula. If the physician opted for the anti-VEGF treatment, the patient received 1.25 mg of bevacizumab intravitreally, following standard procedures. The assessment for re-treatment with bevacizumab was case-specific, taking into account the degree of neovascularisation regression and/or haemorrhage resorption.

Age, sex, type of diabetes, treatment to date, visual acuity at the start of bevacizumab treatment, possible presence of iris neovascularization (rubeosis iridis), number of bevacizumab injections received,

duration of the follow-up, visual acuity at the last follow-up were recorded. We also checked for possible complications in treatment.

Bevacizumab is not registered for intravitreal use. There is no registered medication available in Slovenia for patients with PDR who do not have DME. Bevacizumab is used as a part of the study "Avastin for intravitreal use" (Sl. *Avastin za intravitrealno rabo*), approved by the National Medical Ethics Committee of the Republic of Slovenia. All patients received appropriate oral and written explanations before the start of the treatment and signed a consent to treatment. The study was approved by NMEC (No. 69/11/13), date of approval: December 12, 2013.

## 3 Results

11 patients with PDR and without DME were treated with bevacizumab between May 2011 and May 2019 due to recurrent vitreous haemorrhages: 6 men and 5 women. In all patients, only one eye was treated with bevacizumab. At the start of the treatment, patients ranged in age from 40 to 87 years, with a mean age of 60.7 ± 15.3 years; 4 patients had type 1 diabetes and the remaining patients had type 2 diabetes. All of them had already undergone extensive panretinal laser photocoagulation on the treated eye; one also had a vitrectomy. Also, they all had a central retinal thickness of less than 250 micrometres and normal intraocular pressure on the treated eye. In three patients, rubeosis iridis was present on the treated eye at the start of treatment.

Patients were monitored at 4- to 12-week intervals. In accordance with professional doctrine, vitrectomy was suggested for all of them due to recurrent vitreous haemorrhages, but they did not opt for surgery for various reasons (mostly due to other health problems).

In all of them, the ocular condition improved following bevacizumab injections. 1-6 injections were required to stabilize the condition. The improvement was evaluated by improving visual acuity or resorption of haemorrhage and/or regression of neovascularisations. Treatment was discontinued if fibrotic neovascularisations were clinically visible and there was no fresh vitreous haemorrhage. There was no recurrence in 4 patients during follow-up after discontinuation of treatment (in 2 patients, the condition stabilized already after 1 injection of bevacizumab), and in the remaining 7 patients, the bleeding recurred, and the treatment had to be repeated. The mean best-corrected visual acuity at baseline was 57.2 ± 25.9 ETDRS letters and, during follow-up 6-8 weeks after the last bevacizumab injection, 64.5 ± 16.7 ETDRS letters. Patients were monitored for 1–8 years. The mean number of injections per patient per year of treatment was 2.1 ± 1.1.

At the last follow-up, two patients agreed to have a vitrectomy; the others are monitored by follow-up examinations and, when necessary, they receive further treatment. During the monitoring, none of the patients had a complication associated with the injection itself, nor did any patient develop tractional retinal detachment or a possible serious systemic complication.

Table 1 shows the characteristics of patients with active PDR with vitreous haemorrhage, the treatment to date, the best-corrected visual acuity at the start of treatment and at follow-up 6-8 weeks after the last injection, the treatment period, and the number of bevacizumab injections during this period.

## 4 Discussion

By injecting bevacizumab in patients with PDR who had already undergone extensive panretinal laser photocoagulation and who had not undergone vitrectomy or re-vitrectomy for various reasons, neovascularisation regression was achieved, or rather, PDR progression was prevented during monitoring. No growth of vis-

**Table 1:** The characteristics of patients with active PDR with vitreous haemorrhage, the treatment to date, best-corrected visual acuity at the start of treatment and at follow-up after the last injection, the treatment period and the number of bevacizumab injections during the period.

| Patient | Age (in years) | Gender | Diabetes type | Treatment to date | Rubeosis iridis | BCVA at the beginning of treatment (ETRDS letters) | Number of injections | Monitoring period | BCVA following the last injection (ETRDS letters) | Follow-up treatment |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 40 | m | 1 | PRP | no | 68 | 20 | 2011–2019 | 55 | PPV |
| 2 | 41 | f | 1 | PRP | no | 20 | 13 | 2017–2019 | 53 | monitoring and additional treatment if necessary |
| 3 | 43 | f | 1 | PRP | no | 74 | 1 | 2018–2019 | 71 | monitoring and additional treatment if necessary |
| 4 | 48 | m | 1 | PRP | yes | 81 | 8 | 2014–2018 | 84 | monitoring and additional treatment if necessary |
| 5 | 64 | m | 2 | PRP | yes | 80 | 5 | 2017–2019 | 81 | monitoring and additional treatment if necessary |
| 6 | 66 | m | 2 | PRP | no | 55 | 1 | 2018 | 24 | PPV |
| 7 | 67 | m | 2 | PRP, PPV | no | m.p.b.e. | 6 | 2017–2019 | 60 | monitoring and additional treatment if necessary |
| 8 | 70 | f | 2 | PRP | no | 45 | 6 | 2017–2019 | 67 | monitoring and additional treatment if necessary |
| 9 | 71 | f | 2 | PRP | no | 77 | 5 | 2017–2019 | 78 | monitoring and additional treatment if necessary |
| 10 | 71 | m | 2 | PRP | yes | 70 | 2 | 2017–2019 | 66 | monitoring and additional treatment if necessary |
| 11 | 87 | f | 2 | PRP | no | 58 | 4 | 2017–2019 | 71 | monitoring and additional treatment if necessary |

Legend: DT – diabetes type; M – male; F – female; BCVA – best-corrected visual acuity; PRP – panretinal photocoagulation; PPV – vitrectomy; m.p.b.e. – motion perception before the eye.

ible neovascularisations and progression to tractional detachment was observed in any of the patients, nor did we note a development of neovascular glaucoma.

Recurrent vitreous haemorrhages indicate the presence of active neovascularisations and are an indication for additional laser photocoagulation. Jorge et al. found that anti-VEGF drugs in patients with PDR, in whom regression of neovascularisation is not achieved despite intensive panretinal laser photocoagulation, significantly reduce areas where retinal vascular leakage is present; they also improve visual acuity (12). The combination of panretinal laser photocoagulation and anti-VEGF medication achieved greater regression of neovascularisation in previously untreated patients than in patients treated with panretinal laser photocoagulation alone (13). All of our patients had already undergone extensive panretinal laser photocoagulation; one also had a vitrectomy, but they were still experiencing recurrent haemorrhages.

If the vitreous haemorrhage does not resorb or is recurrent, vitrectomy is required. A panretinal laser photocoagulation, performed beforehand, reduces the chance of haemorrhage after surgery. In cases where panretinal laser photocoagulation or vitrectomy is not possible, anti-VEGF medications may be used as a temporary option. We do not have a registered medication for the treatment of PDR in Slovenia. Bevacizumab is an anti-VEGF medication that is not registered for ocular use, but its efficacy and safety have been confirmed by a number of studies examining the efficacy and safety of treatment in patients with age-related macular degeneration and diabetic macular oedema, as well as in patients with PDR (14-16).

Some smaller studies have described a beneficial effect of bevacizumab on haemorrhage resorption (17-20). A multi-centre, double-blind randomized study of the DRCR.net protocol N compared two groups of patients with extensive vitreous haemorrhage that prevented panretinal laser photocoagulation. The first group of patients was treated with the anti-VEGF medication ranibizumab, and the second group received saline intravitreally. After 16 weeks, there was no significant difference between the groups in the number of patients who required vitrectomy (21), nor was there a difference after one year (22). However, panretinal laser photocoagulation was possible in several patients receiving ranibizumab (22). Haemorrhage resorption and regression of neovascularisations were observed in our patients during treatment; however, the recurrence of haemorrhage was not prevented in all cases. The beneficial effects on vitreous haemorrhage reflect the effect of bevacizumab on neovascularisations, not on the haemorrhaging itself. Bevacizumab triggers the regression of neovascularisation as a VEGF inhibitor. The effect is noticeable already after 24 hours but is only transient (19). Haemorrhage reoccurs when the disease is reactivated.

In recent years, several studies have examined the efficacy of anti-VEGF medication for the treatment of PDR, compared with panretinal laser photocoagulation (23-25). A multicentre study of the DRCR.net S protocol, in which patients with PDR were treated with either ranibizumab or panretinal laser photocoagulation, showed that ranibizumab was not inferior in efficacy to panretinal laser photocoagulation in terms of improving visual acuity after 2, or rather, 5 years. After 2 years, visual acuity was improved in patients treated with ranibizumab compared with visual acuity in patients treated with panretinal laser photocoagulation. Also, peripheral vision loss was lower in these patients; there were fewer vitrectomies due to complications of PDR (vitreous haemorrhage, retinal detachment), and DME developed less frequently (24,26). After 5 years, visual acuity was similar in both groups of patients. Severe visual impairment or serious PDR complications were rare in both groups, but there was less DME in the ranibizumab-treated group. Contrary

to expectations, vision loss impairments progressed in both groups, so that the difference between the groups was smaller after 5 years than after two years. The researchers concluded that both ranibizumab and panretinal laser photocoagulation are good options for the treatment of PDR (25). Similarly, a multicentre CLARITY study compared aflibercept with panretinal laser photocoagulation in patients with PDR. One group of patients with PDR received aflibercept according to the prescribed protocol, and the other group was treated with panretinal laser photocoagulation. The results of this study have also shown that anti-VEGF medication was no less effective compared to panretinal laser photocoagulation in terms of visual acuity. There was a greater regression of diabetic retinopathy in patients treated with aflibercept than in patients treated with panretinal laser photocoagulation. Complete regression of neovascularisations occurred in 64% of eyes treated with aflibercept, whereas complete regression of neovascularisations occurred in only 34% of eyes treated with panretinal laser photocoagulation (23). The results of the treatment of our patients are consistent with the results of these studies.

According to the results of studies such as DRCR.net protocol S and CLARITY and others (10,23,25), anti-VEGF medications are effective and safe for the treatment of patients with PDR. Nevertheless, these encouraging results raise questions about the long-term effects of such treatments, on both systemic and local levels (27). No significant adverse events or complications were reported in our patients, but the follow-up period was short in most cases and the number of injections was low.

Patient involvement is very important in anti-VEGF treatment, as frequent check-ups and re-injections are required. A retrospective cohort study involving 2,302 patients found more than 20% of patient dropout over a 4-year period (28). In a retrospective study of 59 patients who did not come for a follow-up examination after treatment for more than 6 months, the anatomical and functional outcome was worse in those patients who were treated with anti-VEGF medications alone before discontinuation, when compared with patients who have undergone panretinal laser photocoagulation (29). Regular check-ups reduce the risk of vision loss in patients with PDR. The risk is higher in patients treated exclusively with anti-VEGF medications, as the effect of the medications is short-term. Good cooperation is therefore all the more important for these patients. Our patients were motivated and had regular check-ups. Therefore, the deterioration was not a reflection of poorer participation, but a consequence of the activity of the disease.

Given the small number and the large variety of patients, different lengths of treatment and treatment at the discretion of the physician, a more detailed analysis of the treatment success of our patients is not possible. Nevertheless, our data showing the efficacy of bevacizumab in preventing the progression of PDR may contribute to the assessment of the quality of work in the daily clinical practice of individualized treatment of patients for whom we cannot optimally follow current guidelines for various reasons.

## 5 Conclusion

By using bevacizumab, we achieved regression of neovascularisations in our patients and prevented the progression of PDR. Anti-VEGF medications are effective in treating proliferative diabetic retinopathy. Optimum treatment of patients with diabetic retinopathy requires an individualized approach, and anti-VEGF medications may also play an important role in patients with proliferative diabetic retinopathy for whom other treatments are not sufficiently effective or feasible.

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