Intravitreal Bevacizumab in Diabetic Retinopathy

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Abstract

To study the effect of Intravitreal Bevacizumab in proliferative diabetic retinopathy (PDR), the worse eye of 44 cases of diabetic retinopathy underwent intravitreal bevacizumab injection. Focal macular laser or PRP was performed when required for this eye and the fellow eye. Visual acuity, Optical coherence tomography and fluorescein angiographic changes over 9 months were studied. The results were compared with the fellow eye, which underwent laser treatment only.

An improvement in visual acuity and reduction in angiographic leakage were observed in 39 eyes at 9 months follow up. Serial OCT follow up showed decrease of edema in 32 cases of clinically significant macular oedema.

Bevacizumab is very useful and safe as an adjuvant in controlling neovascularisation and macular edema in diabetic retinopathy.

Introduction

Advanced proliferative diabetic retinopathy (PDR) is one of the most important causes of loss of vision in the diabetic patient. Advances in vitreoretinal surgical techniques including laser photocoagulation and vitrectomy systems like wide-angle visualization and silicone oil injections have no doubt increased the results in tractional and combined rhegmatogenous retinal detachments. Different treatment methods, including the perioperative use of heparin and 5-fluorouracil in irrigating fluids during pars plana vitrectomy (PPV), have been tried in an attempt to reduce the incidence of PVR in high-risk proliferative states, but with only limited success. However these have not prevented the occurrence of blindness and these treatment modalities require technology and infrastructure that may not be available or accessible to millions of diabetics living in our subcontinent.

An inflammatory component in retinal neovascular proliferation in PDR and proliferative vitreoretinopathy (PVR) was noted. Machemer and other researchers showed that intravitreal steroid injections, particularly triamcinolone acetonide, were not toxic to the eye and may potentially be important in reducing the intraocular inflammation and vitreoretinopathy caused by fibroblastic proliferation. It is therefore intuitive that intravitreal steroid injections could be beneficial both in PDR with TRD and in PVR. Search for newer agents like targeted monoclonal antibodies were always on. Bevacizumab targets and blocks vascular endothelial growth factor (VEGF) and VEGF’s binding to its receptor on the vascular endothelium.¹ Since VEGF is released by many cancers to stimulate proliferation of new blood
vessels, the combination of bevacizumab and chemotherapy was found to increase objective responses, median time to progression, and survival in patients with metastatic colorectal cancer, compared with chemotherapy alone. The ocular use of this drug has a potential in all the proliferative retinopathies that express VEGF. So it is now being increasingly used in proliferative diabetic retinopathies.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\)\(^,\)\(^4\) as well as in many other diseases like vascular blocks and age related macular degeneration.\(^5\)\(^,\)\(^6\)\(^,\)\(^7\)

Laser photocoagulation has a lot of disadvantages including decreased visual acuity, reduced contrast sensitivity and constricted fields. Our attempt in this study is to underline the effect of chemotherapeutic agents in PDR.

**Methodology**

In a prospective, nonrandomized, interventional case series 44 eyes of 44 diabetic individuals were diagnosed with proliferative diabetic retinopathy. All patients received a detailed counseling of the study design and aims, and were provided with written informed consent. All patients were evaluated and treated by a single retina specialist. Inclusion criteria were patients with type II diabetes, PDR, visual acuity loss, and neovascular leakage shown by fluorescein angiography (Zeiss FF 450 plus, Germany). Eyes with history of glaucoma, cataract extraction, or other intraocular surgery were excluded from the study. Eyes with an epiretinal membrane, posterior hyaloid traction, ischemic maculopathy, and diabetic papillopathy were also excluded. The risks and benefits of the procedure were discussed with each patient before injection, and all patients were provided written informed consent. Baseline parameters were documented including best-corrected visual acuity, central macular thickness, intraocular pressure (IOP) and lenticular status. The best-corrected visual acuity was determined from the Early Treatment Diabetic Retinopathy Study (ETDRS) chart and calculated as logarithm of minimal angle of resolution (logMAR). Central macular thickness was measured by optical coherence tomography (OCT4; Zeiss). Optical coherence tomography (OCT) was performed by acquiring six radial scans, 5 mm long, centered on the fovea, and then analyzed with retinal map protocol. Intraocular pressure was measured by applanation tonometer. Care was taken to see that systemic conditions of the patients were under control (blood glucose, blood pressure, and general condition), and they were receiving oral hypoglycemic agents or insulin for glycemic control.

All patients underwent fluorescein angiography and optical coherence tomography and the eye with more angiographic leakage or vitreous hemorrhage was designated to the bevacizumab arm of the study. These patients were informed regarding the drug and its side effects; and an informed consent was obtained from all of them. The worse eye received bevacizumab intravitreal injection and panretinal photocoagulation, while the better eye received panretinal photocoagulation only.

All 44 eyes meeting these eligibility criteria received a single intravitreal injection containing 1.25 mg of commercially available bevacizumab in 0.05 ml. Data analysed was collected for each patient at the preoperative visit and at 1 month, and 9 months post injection. A total of 44 eyes (28 right eyes, 16 left eyes) were identified, of 44 patients (27 males, 17 females). The mean age was 52.3 years (range of 22–72 years) and the mean follow-up time was 10.3 months (range of 9–12 months). All operations were performed by a single surgeon (G.S.P.) using the same surgical techniques. An unaltered, commercially available 0.05 mL solution containing 1.25 mg of bevacizumab was injected into all eyes through a sclerotomy towards the 6 o’clock position. Subconjunctival injections of antibiotics and steroids was also given in all patients. The outcome measures were studied at 1 month and 9 months, which included visual acuity, angiographic leakage on FFA, retinal thickness on OCT and any side effect profile that we thought to be due to intravitreal bevacizumab.

Angiographic leakage was graded as absent (grade1), present mildly (grade2) and gross leakage (grade3). Central macular thickness was used for statistical analysis in the OCT.

**Results**

All 44 patients had a diagnosis of proliferative diabetic retinopathy. 25 patients had coexisting hypertension. Nineteen eyes had some areas of vitreous hemorrhage to start with. Seven eyes were pseudophakic prior to
this intervention, 4 eyes had cataract, and 33 eyes had clear lenses.

None of the injections were associated with any significant pain or morbidity; there was mild subconjunctival hemorrhage in 6 patients, which resolved with in a week. The IOP was normal on the first postoperative day for all patients.

The mean logMAR visual acuity significantly improved from 0.8 ± 0.16 at baseline to 0.6 ± 0.14 at 1 week, 0.6 ± 0.13 at 1 month, and 0.6 ± 0.11 at 9 months in the bevacizumab arm of the study. (p<0.05)

In the other eye, the mean visual acuity remained stabilized without any statistical change from 0.5 ± 0.13 to 0.5 ± 0.13 at 1 month, and 0.5 ± 0.14 at 9 months. (p=0.95)

Angiographic leakage reduced significantly in all patients who underwent the bevacizumab injection from grade 3 to grade 1 at the end of 1 month, but increased to grade 2 by the end of the study. In the PRP arm, the angiographic leakage reduced from grade 3 to grade 2 in 23 eyes, but in all the others the leakage persisted at grade 3. (Fig. 1 a & b).

OCT thickness reduced significantly by 112 ± 36 microns in all patients who underwent bevacizumab (Fig. 2) injection at the end of 1 month and by 136± 23 by the end of the study. (p<0.05). (Fig. 2 a & b).

OCT thickness had stabilized without statistical change in the PRP arm of the study. The change in macular thickness at 1 month was 21 ± 17 microns and at 9 months was 27 ± 21 microns (p=0.98).
No side effects were noted in any of the patients receiving bevacizumab.

The mean baseline IOP was $14.7 \pm 2.0$ mmHg (range 12–18 mmHg), and at 1 week, 1 month, and 9 months after injection were $15.9 \pm 2.1$ mmHg (range 12–20), $15.7 \pm 2.4$ mmHg (range 12–20), and $15.3 \pm 2.3$ mmHg (range 12–18) respectively.

**Discussion**

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF) initially described for metastatic colorectal cancer. VEGF is implicated in the genesis of neovascularisation in the retina in almost all vasculopathies of the retina including diabetic retinopathy, age related macular degeneration etc. Since bevacizumab was found to give good results in these cases in the eye, it has been used for a variety of retinal diseases.

The visual acuity in all eyes, which underwent bevacizumab injection, showed a significant increase. The angiographic leakage disappeared to almost negligible levels by the end of one month and remained like that through out the study. Taking into consideration the fact that the worse affected eye was enrolled into the study it is of importance to note that none of the 44 eyes, which received bevacizumab, needed to be operated upon for vitreous hemorrhage or traction retinal detachment.

Macular edema subsided significantly with bevacizumab. A change of central macular thickness of 112 microns was documented by the first month and that drop in thickness increased to 136 microns by the end of the study. There was no statistical change of the macular thickness in the PRP arm of the study. Thus macular edema occurring in PDR in this study was taken care of by bevacizumab.

Bevacizumab is a versatile monoclonal antibody, which may be complimentary to laser photoacoagulation and surgery in advanced cases of proliferative diabetic retinopathy. The ease of the injection procedure and the availability and affordability makes it a very useful drug in the management of diabetic retinopathy.

The other anti VEGF agents used in the eye are pegaptanib sodium and ranibizumab, both of which have undergone large multicentered clinical trials in the management of age related macular degeneration. Clinical trials to evaluate whether their use in diabetic retinopathy can give better results than bevacizumab may be of great help. Till then, bevacizumab will remain a significant barrier between diabetic retinopathy and blindness.

Advances in nano medical and pharmaceutical technology is making definite steps to improve our surgical results in diabetic retinopathy and in many other ocular diseases.

**References**