Diabetic retinopathy (DR) is a major cause of visual loss in patients with diabetes mellitus. Diabetic macular edema (DME), which can occur at any stage of DR, is characterised by increased vascular permeability and the deposition of hard exudates at the central retina. Diabetic macular edema is now the principal cause of vision loss in people with diabetes (1).

Bevacizumab (Avastin™, Genentech Inc. San Francisco, California, USA) is a full length humanized antibody that binds to all subtypes of vascular endothelial growth factor (VEGF) and has been approved by the US Food and Drug Administration for the treatment of metastatic colorectal cancer (2). Recent reports have suggested that bevacizumab may be useful for the treatment of choroidal neovascularization (CNV), diabetic macular edema, DR and macular edema associated with retinal venous occlusive diseases (3-5).

The purpose of this study was to report the efficacy of intravitreal injections of bevacizumab by measuring visual acuity (VA) and foveal retinal...
thickness (RT) after intravitreal injection of bevacizumab for DME.

METHODS

We retrospectively reviewed 20 eyes of 19 consecutive Japanese patients (12 males, 7 females) with DME treated with intravitreally administered bevacizumab. The patients were followed for four weeks at Tokushima University Hospital. The Ethical Committee of the University of Tokushima approved the off-label use of bevacizumab. The decision to treat with intravitreally administered bevacizumab was made by the patient after a complete discussion on its risks, benefits and alternative treatments. If the patient decided to proceed with bevacizumab therapy, they signed a consent form before administration.

The eye was prepared with a topical anesthetic and a drop of antibiotic before the injection. The eyelid margin was prepared with a povidone/iodine solution. A wire speculum was placed followed by several drops of diluted povidone/iodine solution to the conjunctiva at the injection site. An injection of 1.25 mg of bevacizumab (0.05 ml of bevacizumab at a concentration of 25 mg/ml) was administered using a 30 gauge needle from the pars plana.

Patients were examined at baseline, at one week, two weeks, and four weeks. We recorded the BCVA measured with a Japanese standard decimal VA chart and calculated the mean BCVA using the logarithm of the minimum angle of resolution (logMAR) scale, intraocular pressure (IOP), and fluorescein angiography (FA). Analysis of retinal anatomic features was performed using an optical coherence tomography (OCT, Stratus III OCT; Carl Zeiss, Dublin, California, USA). The RT at the fovea of the 1-mm central retina was determined using six low-resolution diagonally oriented fast macula scans.

Statistical analysis was performed using the Student’s t-test to compare the VA, IOP and the central RT at one, two, and four weeks from baseline.

RESULTS

Twenty eyes of 19 patients (12 males, 7 females) with DME were studied. The ages of the patients ranged from 44 to 76 years with a mean of 59.7±8.0 years. All patients had type II diabetes. There was no history of any other ocular disease except for refractive errors or cataracts. All patients had panretinal photocoagulation. Three patients had sub-Tenon’s capsule injection of 20 mg triamcinolone acetonide (TA). Nine patients had cataract surgery with intraocular lens implantation, and nine patients had vitrectomy. The glycosylated hemoglobin (HbA1c) averaged 7.1±1.1 before starting the study (Table 1).

The BCVA at one week improved by two lines or more in six eyes (30%) (Figure 1) and the BCVA at...
four weeks improved in nine eyes (45%) (Figure 2). No significant improvement in the mean BCVA from baseline was observed at one week (P > 0.05), or four weeks (P > 0.05). FA showed resolution of leakage in some eyes.

During the follow-up of the patients in this study, no complications such as inflammation, increased IOP (Figure 4), severe vision loss, endophthalmitis, or systemic events were observed.

DISCUSSION

DME has been characterized by inflammation, including intravitreal induction of proinflammatory cytokines (6), intraretinal expression of proinflammatory caspases (7) and mediators. Many clinical investigators have found that an intravitreal injection of TA may reduce macular edema. However, the use of intravitreal TA may lead to complications such as increased IOP, progression of cataract and endophthalmitis (8).

Bevacizumab is an anti-VEGF agent that is approved for the treatment of disseminated colorectal cancer but is not licensed for intraocular use. However, bevacizumab appears to show a similar efficacy for the treatment of DME and proliferative DR (9).

VEGF has been shown to be an endothelial cell-specific mitogen and an angiogenic inducer. It is also a vascular permeability factor; it has been demonstrated to increase the permeability of retinal vessels by increasing the phosphorylation of tight junction proteins (10). It was found that the concentration of VEGF in the vitreous increased and correlated with the severity of macular edema in patients with DME (11), therefore anti-VEGF therapy is expected to show a dramatic reduction of DME. Bevacizumab has attracted interest because of its low cost; however systemic safety is not approved.
We conformed to the widely used concentration of the drug (1.25 mg bevacizumab) in this study. Anti-VEGF therapy of the intravitreally administered bevacizumab showed a marked reduction of macular edema soon after the injection at one week. However, recurrence of macular edema occurred within four weeks. A retinal penetration study revealed the absence of bevacizumab four weeks after the injection (14), which may suggest the limited effect of bevacizumab on suppression of VEGF activity.

Mean retinal thickness was reduced at one week after the injection (P<0.05). However, no significant improvement in the mean BCVA. It is possible that visual acuity may not improve with the same time course as thickness of the macula. It depends on macular function improvement and it may have timelag (15).

Maia, et al. reported that a combination therapy of intravitreal triamcinolone and laser photoagulation decreased DME (16). Recently, a combination therapy with intravitreal bevacizumab and photodynamic therapy (PDT) for CNV in patients with AMD has been reported to improve VA and anatomic changes and reduce retreatment rates (17). Therefore, we think that the combination of laser photoagulation with intravitreal bevacizumab may improve BCVA and decrease RT more than laser photoagulation alone or intravitreal bevacizumab alone for the treatment of moderate DME.

In summary, the therapy of intravitreal bevacizumab alone for DME is effective in the short-term, however it is not effective in the long-term.

REFERENCES

15. Diabetic Retinopathy Clinical Research Network : Relationship between optical coherence
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