

Intravitreal Bevacizumab with or Without Triamcinolone for Refractory Diabetic Macular Oedema

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ABSTRACT

We evaluate the effect of intravitreal injections of Bevacizumab (IVB) alone or combined with triamcinolone (IVT) in the first injection for treatment of refractory diabetic macular oedema (DME). Sixty eyes of sixty patients with refractory DME were included. Half of the receive injections of IVB (1.25 mg/0.05 mL) or combined IVB and IVT (1.25 mg/0.05 mL and 2 mg/0.05 mL respectively). The primary outcome measure was change in central macular thickness (CMT). Secondary outcome measures were change in best-corrected logMAR visual acuity (BCVA) and incidence of potential adverse events. Central macular thickness was reduced significantly in both the IVB and IVB/IVT groups. At week 24, CMT change compared to the baseline was $-95.7 \mu\text{m}$ (95% CI, -172.2 to -19.26) in the IVB group and $-92.1 \mu\text{m}$ (95% CI, -154.4 to -29.7) in the IVB/IVT group. There was not a significant difference between the IVB and the IVB/IVT groups ($p=0.022$). Improvement of BCVA was initiated at weeks 6 and 12 in the IVB/IVT and IVB groups respectively. In terms of BCVA change compared to the baseline at 24 weeks, the differences between the IVB and the IVB/IVT groups ($p=0.006$) were significant. Anterior Chamber reaction was noticed in six (20%) and six (20%) eyes respectively in the IVB and IVB/IVT groups the day after injection, and it resolved with no sequel. Elevation of IOP occurred in two eyes (6%) in the IVB/IVT group. Intravitreal injections of Bevacizumab had a beneficial effect on refractory DME in terms of CMT reduction and BCVA improvement. Addition of triamcinolone in the injection seemed to induce earlier visual improvement; however, it did not show any significant additive effect later during follow-up.

Key words: bevacizumab, diabetic macular oedema

Introduction

Macular oedema is a predominant cause of visual impairment in diabetic patients. The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that focal laser photocoagulation is effective in reducing the risk of visual loss in eyes with clinically significant macular oedema¹. Laser treatment, however, has limited results in eyes with diffuse diabetic macular oedema (DME)^{1,2}. The poor response of diffuse DME to laser photocoagulation has prompted interest in other treatment modalities. Multiple studies have shown that a single intravitreal injection of triamcinolone acetonide (IVT) may have a rapid effect in eyes with diffuse diabetic macular oedema resistant to laser therapy. This therapeutic ef-

fect, however, decreases with the disappearance of intravitreal triamcinolone³⁻⁵.

Recent research has revealed the role of the vascular endothelial growth factor (VEGF) in inducing vascular hyper permeability^{5,6}. It has been shown that vitreous samples from eyes with DME show elevated VEGF levels⁵.

According to these findings, anti-VEGF medications may have a critical role in prevention and/or treatment of DME. A recent clinical trial revealed the beneficial effect of pegaptanib on diabetic macular oedema⁷. Bevacizumab, a humanized full-length monoclonal antibody

that inhibits all isoforms of VEGF, has also been used for treatment of refractory DME.

We conducted randomized clinical trial to evaluate the morphological effect of three repeated injections of intravitreal Bevacizumab (IVB), either alone or in combination with triamcinolone acetonide in the first injection, for the treatment of refractory DME^{8–11}. The 24-week results of this clinical trial are presented in this report.

Materials and Methods

The study protocol was explained to all patients, and informed consent was obtained. Patients were referred to the Ophthalmic Research Center by co investigators in the participating centers.

Participants

Eyes with clinically significant macular oedema unresponsive to previous macular laser photocoagulation, with the last session being more than 3 months prior, were included.

Exclusion criteria consisted of visual acuity =20/40, history of cataract surgery within the past 6 months, prior intraocular injection or vitrectomy, glaucoma or ocular hypertension, proliferative diabetic retinopathy (PDR) with high-risk characteristics, vitreous hemorrhage, significant media opacity, and presence of traction on the macula. Monocular patients were excluded. Pregnancy and serum creatinine level =3 mg/100 were also among the exclusion criteria.

Interventions

All participants were questioned about the duration and management of their diabetes mellitus, history of systemic hypertension, smoking, and panretinal photocoagulation (PRP). Dates of previous macular laser photocoagulation were recorded. Best corrected visual acuity (BCVA), presence and extent of neovascularization of iris (NVI), degree of lens opacity in phakic eyes, intraocular pressure (IOP), and severity of diabetic retinopathy were also recorded. Best corrected visual acuity (BCVA) measured by Snellen chart was recorded by the logarithm of the minimum angle of resolution (logMAR). Lens opacity was graded from 0 to 4+ by observers using the Lens Opacities Classification System III (LOCS III) for each of three different categories including nuclear sclerosis, posterior sub capsular opacities, and cortical cataract⁴. The anterior chamber inflammatory reaction was evaluated using slit lamp bio microscopy. The extent of NVI and severity of diabetic retinopathy were expressed in clock hours and ETDRS scaling respectively. Baseline ancillary diagnostic tests including fundus photography, fluorescein angiography (FA), and optical coherence tomography (OCT) were performed before intervention. Fundus photography was performed with a Topcon Fundus Camera (TRC-NW7SF) using a 50° field centred on the fovea. Optical coherence tomography was performed

by a trained optometrist using commercially available equipment spectral OCT (OTI, Canada). All OCT scans were acquired using macular thickness map protocol by a standard mode and proper scanning centralization. The OCT examination was comprised of six radial 6 mm-long scans of each eye centered on the patient's fixation point. This mapping averaged the six scans to give the central macular thickness (CMT) in a central area 1 mm in diameter. The same protocol was repeated at each follow-up visit. To reduce the effect of diurnal variation on macular thickness measurement, all scans were performed between 9 and 11 a.m. Eligible eyes were randomly assigned to one of the two study arms, which utilised intravitreal Bevacizumab (IVB group), combined intravitreal Bevacizumab and triamcinolone (IVB/IVT group).

Surgical technique

Injections were done under sterile conditions with topical anesthesia and insertion of a lid speculum. For the IVB group, 1.25 mg (0.05 cc) Bevacizumab (Avastin, Roche Pharma AG), was injected intravitreally with a 30-gauge needle through the superotemporal quadrant. For the IVB/IVT group, there is a mixture in one syringe e.g. 1.25 mg Bevacizumab and 2 mg (0.05 cc) triamcinolone acetonide (Triaminject, WINTHROP, Germany) was injected intravitreally through the superotemporal quadrant.

Second and third injections of the IVB/IVT group consisted of only Bevacizumab (1.25 mg) according OCT finding. All eyes underwent an ophthalmic examination, checking 1 and 7 days after each injection for anterior chamber (AC) reaction and IOP rise. Complete ophthalmologic examination and OCT were performed before the second and third injections, and at 18 and 24 weeks after the first intervention. Fluorescein angiography was repeated at 24 weeks after the initial intervention.

Outcome measures

The primary outcome measure was change in CMT compared to baseline. Central macular thickness was defined by the average thickness of a central macular region 1,000 mm in diameter centered on the patient's foveola. Secondary outcome measures included change in best-corrected logMAR visual acuity, IOP rise, cataract progression, intraocular inflammation, and any other serious adverse effect.

Randomization

Randomization was performed using a random block permutation method according to a computer-generated randomization list. The block lengths varied randomly^{1,12}. A random allocation sequence was performed by a biostatistician. Details of the series were unknown to the investigators. Masking Subjects were masked to the treatment modality.

Sample size

To have a power of 90%, a level of significance equal to 0.05 and an assumed standard deviation of 50 mm, a minimum sample size of 30 eyes for each arm was calculated to detect a 30% difference in CMT changes between the two treatment groups.

Statistical analysis

Patient data was recorded in data collection sheets. Statistical analysis was performed with SPSS software (Statistical Package for Social Sciences version 13.0, SPSS Inc. Chicago, IL, USA). Qualitative variables were expressed. Using percentages and quantitative data were explained with mean, standard deviation, and/or confidence interval. T-test, chi-square test, and analysis of variance (ANOVA) were used for inferential statistics. A normal distribution of the quantitative data was checked using the Kolmogorov-Smirnov test. The level of significance was 0.05 (p=0.05). To rule out the possible effect of the intravitreally injected drug(s) on the other eye, all statistical analyses were repeated after excluding patients with both eyes in the study.

Results

Sixty eyes of 60 patients were assessed for eligibility criteria. The mean (±SD) age of patients was 59.7±8.3 years (range, 39–74 years). Twenty nine patients (48%) were male and 31 (52%) were female. There was a history of cataract surgery in 3 eyes (10%). Nonproliferative diabetic retinopathy (NPDR) was present in 24 eyes (80%), early proliferative diabetic retinopathy in two eyes (6%),

and regressed proliferative diabetic retinopathy in 3 eyes (10%). Iris neovascularization was not detected in any eye at presentation. History of smoking and systemic hypertension was positive in 3 (10%) and 10 (30%) patients respectively. The eligible eyes were randomized into two groups: 30 eyes in the IVB group, 30 eyes in the IVB/IVT group. Mean HbA1c level was 9.95 mg/dL in the IVB group, 9.35 g/dL in the IVB/IVT group. In terms of diabetes control, 20.3% and 27.6% of patients were on insulin in the IVB and IVB/IVT groups respectively. There was no significant difference among the groups regarding the above-mentioned parameters. The groups were matched for age, sex, baseline visual acuity, systemic hypertension, history of smoking, stage of diabetic retinopathy, number of previous laser sessions at the macula, and history of PRP (p>0.05). However, the groups were not matched for CMT before treatment. Statistical analyses were performed after adjustment of the parameters according to their baseline values. Mean of changes in CMT and BCVA in each follow-up visit compared to the baseline are presented in Table 1. The difference between initial and the treatment groups in terms of CMT changes appeared 6 weeks after the first injection, and persisted until 24 weeks. Considering BCVA changes, significant improvement was initially observed at weeks 6 and 12 in the IVB/IVT and IVB groups respectively. Changes in BCVA remained statistically significant for both treatment groups up to 24 weeks (Table 2). At week 24, CMT change compared to the baseline was -95.7 μm (95% confidence interval, -172.2 to -19.3) in the IVB group, -92.1 μm (95% confidence interval, -154.4 to -29.7) in the IVB/IVT group. ANOVA and subsequent pairwise comparison tests (using the Bonferroni test) showed no sta-

TABLE 2
MEAN DIFFERENCES OF CMT AND BCVA CHANGES IN A PAIRWISE COMPARISON AMONG THE GROUPS AT EACH FOLLOW UP VISIT

| | Intervention (I) | Intervention (J) | BCVA (logMAR) | | CMT(μ) | |
|---------|------------------|------------------|-----------------|---------|------------------|---------|
| | | | Mean diff.(I-J) | p value | Mean diff. (I-J) | p value |
| Week 6 | IVB | IVB/IVT | 0.08±0.04 | 0.169 | 4±27 | 0.999 |
| Week 12 | IVB | IVB/IVT | 0.06±0.06 | 0.994 | 31±27 | 0.786 |
| Week 18 | IVB | IVB/IVT | 0.002±0.06 | 0.999 | 62±35 | 0.253 |
| Week 24 | IVB | IVB/IVT | 0.02±0.06 | 0.999 | -3±42 | 0.999 |

BCVA – Best corrected visual acuity, CMT – Central macular thickness, IVB – Intravitreal bevacizumab, IVT – Intravitreal triamcinolone

TABLE 1
MEAN (±SD) OF CHANGES IN CENTRAL MACULAR THICKNESS AND BEST CORRECTED VISUAL ACUITY IN RELATION TO THE BASELINE

| | Base line | 6 weeks | 12 weeks | 18 weeks | 24 weeks |
|---------------------|-----------|-----------|----------|----------|----------|
| CMT change(μ) | IVB | -87.7±114 | -70±134 | -50±104 | -94±170 |
| | IVB/IVT | -92±140 | -101±110 | -112±120 | -93±124 |
| BCVA change(logMAR) | IVB | -0.75±0.1 | -0.1±0.2 | -0.2±0.2 | -0.2±0.2 |
| | IVB/IVT | -0.1±0.2 | -0.2±0.2 | -0.2±0.2 | -0.2±0.2 |

BCVA – Best corrected visual acuity, CMT – Central macular thickness, IVB – Intravitreal bevacizumab, IVT – Intravitreal triamcinolone

tistically significant difference between the IVB and the IVB/IVT ($p=0.99$) groups (Table 2). BCVA change at week 24 compared to the baseline BCVA was -0.18 logMAR (95% confidence interval, -0.29 to -0.08) in the IVB group, -0.21 logMAR (95% confidence interval, -0.30 to -0.12) in the IVB/IVT group. Mild anterior chamber reaction was noted in four (13%) and five (16%) eyes respectively in the IVB and IVB/IVT groups the day after injection, and it resolved completely in all within 1 week with no treatment. Marked anterior chamber reaction occurred in one eye in the IVB group, which resolved with topical corticosteroid and cycloplegic drops. Two eyes (6%) in the IVB/IVT group showed an IOP rise to 23, 22, and 28 mmHg respectively, at 6, 12, and 18 weeks. The elevated IOP was controlled with an anti-glaucoma drop. Progression of fibrous proliferation was noticed in one eye (3%) of the IVB group with no sign of retinal traction. In none of the eyes was iris neovascularization detected. No progress in lens opacity was detected during the follow-up period.

Discussion and Conclusion

We conducted a randomized clinical trial to evaluate the effect of intravitreal Bevacizumab with or without triamcinolone on refractory diabetic macular oedema. The 24-week results of this study revealed the efficacy of Bevacizumab alone or in combination with triamcinolone acetonide in reducing central macular thickness. Six weeks after the first intravitreal injection, CMT was reduced significantly in both the IVB and IVB/IVT groups. This effect was also apparent 24 weeks after initiation of the study, which corresponded to 12 weeks after the third intravitreal injection. Although there was no significant difference between the IVB/IVT and IVB groups in terms of changes in BCVA throughout the follow-up period, the beneficial effect of the IVB/IVT group appeared earlier compared with the IVB group. Thereafter and up to final follow-up (week 24), both treatment groups maintained their significant effect on visual acuity. Intravitreal bevacizumab has recently gained popularity for treatment of neovascular age-related macular degeneration (AMD). Diabetic macular oedema and neovascular AMD have common VEGF-induced pathogenic pathways. Blood-ocular barrier breakdown and hyperpermeability are present in both of these disorders. Inhibition of VEGF by a pan-anti-VEGF drug may explain the beneficial effect of bevacizumab when used alone or in combination with triamcinolone acetonide in DME. Recently, the effect of primary intravitreal Bevacizumab on DME was evaluated retrospectively in 78 eyes of 64 patients¹³. This treatment resulted in stability or improvement of visual acuity, OCT, and FA at 6 months. A second injection was required in six eyes (20%) and a third injection was needed in three eyes (10%). Patients included in our study had an intractable form of DME with severe visual disturbance and less favorable visual outcome compared with cases of primary DME. Considering the severity of DME and in the attempt to maximize the potential effect

of Bevacizumab, we decided to perform three consecutive injections as a loading dose in our treatment strategy. However, we limited intravitreal triamcinolone to a single injection to reduce the potential side-effects of this medication. Haritoglou et al. performed a prospective noncomparative case series study evaluating the effect of 1.25 mg intravitreal Bevacizumab on refractory DME⁸. The treatment effect was achieved with at least two intravitreal injections of Bevacizumab in most of their patients. The results of their study were comparable with those of the IVB group in our clinical trial in terms of visual improvement and CMT reduction. Therefore, we repeated the statistical analysis excluding patients with both eyes in the study and the same results were obtained. The beneficial effect of triamcinolone acetonide on refractory DME has already been demonstrated in several studies^{3,4,13–19}. We decided to add IVT to IVB in order to possibly attain more therapeutic effect. Our study demonstrated no additive effect by IVT in terms of anatomical results. However there was a trend toward earlier functional effects with combined treatment. Intravitreal Bevacizumab alone nevertheless showed the same therapeutic effect 12 weeks after initiation of treatment. Triamcinolone induced ocular hypertension developed in two eyes (6%) in the IVB/IVT group, which was controlled with topical medications. In a study evaluating the effect of intravitreal Bevacizumab on anterior chamber inflammatory activity in patients with neovascular AMD, none of the patients had a significant, clinically detectable inflammatory response within 1 week of injection⁷. In our study, however, mild anterior chamber reaction occurred in nearly one-fifth of the eyes in the IVB and IVB/IVT groups. It disappeared spontaneously in all eyes within 1 week. No major injection-related complication was noticed in our patients. Considering the relatively short follow-up period, this study is not informative regarding the cataractogenic effect of triamcinolone. The rate of cataract progression has been reported to be 43% in a study with multiple IVT injections and 2 years follow-up⁴. Snellen chart was used for measurement of BCVA. However, inherent shortcomings of this chart, such as non-geometric progression of letter size, variable number of letters per line and lack of a standardized scaling system, should be kept in mind. In summary, three consecutive injections of intravitreal Bevacizumab resulted in CMT reduction and visual improvement in eyes with refractory diabetic macular oedema. These anatomic and functional effects were revealed in the setting of a clinical trial, which to our knowledge is the first study of its kind in the literature. The anatomic effect appeared 6 weeks after the first injection, and was maintained up to 12 weeks after the third injection. Addition of triamcinolone had no significant effect on anatomic results, but resulted in a trend toward earlier visual improvement. Further studies with longer follow up are needed for evaluation of anatomic and functional results and the need for repeat intravitreal injections after 24 weeks.

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KLINIČKA PRIMJENA INTRAVITREALNO BEVACIZUMABA I U KOMBINACIJI S TRIAMCINOLONOM U DIJABETIČKOM MAKULARNOM EDEMU

SAŽETAK

Rađena je klinička studija intravitrealne primjene preparata bevacizumaba, kao i u kombinaciji s triamcinolonom. Rezultati su praćeni analizom OCTa, mjereći debljinu retine u makuli, te oštine vida. U ovom kliničkom eksperimentu dokazano je da je najefektivnija primjena intravitrealno bevacizumaba, te da kombinacija s triamcinolonom nema bitno bolji efekt.