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Effects of intravitreal bevacizumab injection on the clinical manifestations of nonproliferative diabetic retinopathy in patients with macular edema: a systematic review

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ABSTRACT

Introduction: Bevacizumab (Avastin) is considered as an effective strategy in the treatment of various ocular diseases. As a vascular endothelial growth factor (VEGF) inhibitor, Avastin is used to control macular edema in patients with nonproliferative diabetic retinopathy (NPDR). Therefore, in this study, we systematically reviewed the effects of intravitreal bevacizumab injections on nonproliferative stage of diabetic retinopathy.

Methods: Scopus and PubMed were systematically searched to find articles in which the effect of Avastin (bevacizumab) had been evaluated in nonproliferative stage of diabetic retinopathy. Literature search was performed using "Avastin OR bevacizumab", "nonproliferative stage" and "diabetic retinopathy" as keyterms in the title, keywords, and abstract.

Result: All 47 articles were found in all databases, two additional records were found through reference list screening, and only 10 articles were relevant to the purpose of this study. According to the inclusion/exclusion criteria, 39 articles were excluded in several step processes of article selection. The results revealed that intravitreal injection of bevacizumab could be safely used to treat various ocular disease, particularly NPDR stage of diabetic retinopathy with macular edema.

Discussion: Bevacizumab is considered as a novel and effective modality in the treatment of various ocular diseases such as retinal neovascularization, neovascular glaucoma, macular edema, and other ocular complications. Findings also suggested that bevacizumab is a suitable therapeutic approach in clinical use.

Conclusion: According to the results of included documents, intravitreal injection of bevacizumab could be considered as a promising treatment modality in the clinical management of NPDR stage of diabetic retinopathy.

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Introduction

Diabetic retinopathy is one of the most common leading causes of blindness in the world among the people with age range of 20 to 64 years (1). Ischemia that is a known leading cause of neovascularization, diabetic macular edema and macular ischemic changes, is responsible for visual loss in patients with diabetes (2). Measures that can be performed to prevent blindness in these patients are medical controls including control of blood sugar, blood pressure, lipids, and ophthalmic procedures such as laser photocoagulation and pars plana vitrectomy (3). Despite numerous treat-

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ments, diabetic retinopathy is one of the causes of blindness and impaired vision in adults (4). Diabetic retinopathy is divided into two main stages, including proliferative (PDR) and nonproliferative diabetic retinopathy (NPDR). In NPDR, microvascular changes is limited to the retina, and lesions do not exceed the internal limiting membrane (ILM). Specific findings in NPDR include microaneurysms, lack of blood supply to the retina, nerve fiber layer infarcts, hemorrhages in the retina point, edema of the retina, arterial abnormalities, and venous dilatation (5,6). Although many patients loss their visions in the proliferative stage of PDR; 80% of vision loss occurs in NPDR (7). Diabetic retinopathy is responsible for approximately 12% to 14% of new cases of blindness annually (7). Some epidemiological studies have shown that approximately 700,000 people in the United States suffer from PDR, and 500,000 people suffer from diabetic macular edema. Moreover, almost 65,000 new PDR cases and 75,000 new cases of diabetic macular edema are reported each year (7).

Avastin (Bevacizumab) is a monoclonal antibody that could bind to all isomers of vascular endothelial growth factor (VEGF). Intravenous injection of Avastin has been approved by the Food and Drug Administration (FDA) in 2004 for the treatment of colorectal cancer (8). Since most cases of diabetic retinopathy are NPDR, finding a method to prevent the progression of NPDR to the PDR stage and to avoid subsequent visual complications seems reasonable. Most clinical manifestations of NPDR are due to increased vascular permeability. Furthermore, due to increased levels of VEGF in posterior segment of patients with diabetic retinopathy, these manifestations may be associated with increased levels of VEGF in the vitreous.

On the other hand, every therapeutic agent with anti-VEGF property could be of great importance in the treatment of diabetic macular edema (9). Avastin as an effective and novel therapeutic agent is a VEGF inhibitor, and it is used to control macular edema in patients with NPDR (10). Therefore, in the present study, we systematically reviewed the effects of intravitreal bevacizumab (IVB) injections on NPDR.

Methods

Literature search strategy

We systematically searched Scopus and PubMed to find articles in which the effect of Avastin (bevacizumab) had been evaluated on NPDR as a new therapeutic agent. Literature search was performed on 1 April 2015 using "Avastin OR bevacizumab", "nonproliferative stage" and "diabetic retinopathy" as keyterms in the title, keywords, and abstract. The following search strategy, ((intravitreal bevacizumab OR Avastin)) AND (non-proliferative diabetic retinopathy OR nonproliferative diabetic retinopathy), was used to find related documents in English language. Relevant documents were selected independently by two reviewers and data was analyzed regarding the effects of Avastin on NPDR. Moreover, we searched Google scholar as well as the reference list of relevant articles manually to include other relevant documents and to minimize the possibility of any missing data.

Study selection

No time limitation was defined for article selection in literature search; however, in order to avoid any possible misinterpretation of extracted data in subsequent processes of data extraction, we only selected articles in English language. Articles with various types of medical design including the cross-sectionals, case reports, case-controls, clinical trials, and prospective cohort studies were included in this literature review. Nevertheless, we excluded review articles and meta-analysis in the first step of article selection process. We also excluded articles if they were unrelated to the main purpose of this study, or if the study had been conducted on animals. Inclusion criteria were those papers in which the effects of Avastin had been evaluated in NPDR. By reviewing the title, keywords, and abstract of the papers, we omitted duplicated and irrelevant documents in the first step. As well, full texts of the relevant articles were entirely reviewed and used for extraction of desired data.

Data extraction

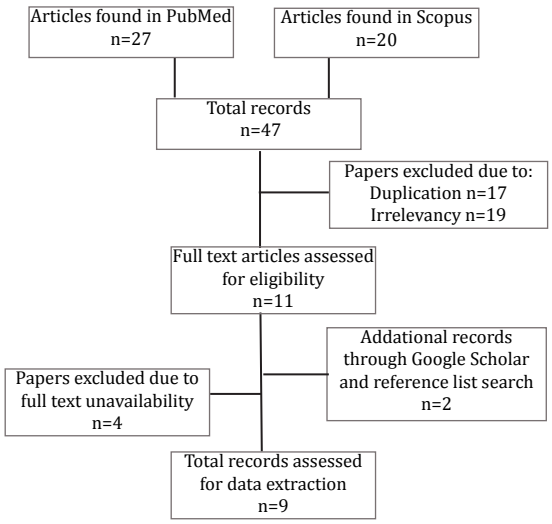
All available data including name of the first author, publication date, study design, country, and main findings of each study were extracted and categorized based on the main purpose of this study. Additional data including the total number of participants, sex ratio, and age, as well as other demographic information of studied population and methods of assessment were obtained as possible. Different methods including optical coherence tomography and fundus fluorescein angiography had been used in the included studies to evaluate variables such as central macular thickness (CMT), visual acuity (VA), and foveal avascular zone (FAZ). We categorized the extracted data based on the results reporting the effects of Avastin on NPDR. All the processes of data synthesis, data analysis, and study selection, which were based on the recommendation of PRISMA 2009 checklist were performed by two independent reviewers (11).

Results

search results

From overall 27 article found in PubMed, and 20 records found in Scopus, almost 18 articles were omitted due to irrelevancy. Seventeen additional records were also excluded in subsequent steps by step processes of article selection due to duplication, language, or subject irrelevancy. Four articles were also excluded due to full text unavailability. On the other hand, two additional records were found through reference list screening and Google Scholar search. By carefully reviewing the articles, only 10 papers, which fully met the inclusion criteria, were used for further assessment and data analysis. Hence, full texts of the included articles were collected, and the desired data were extracted based on the main purpose of this study. Figure 1 shows step by step selection process of the articles.

Figure 1. Flowchart of study selection



Description of the included studies

In the included documents, total of 413 patients with diabetic retinopathy and diabetic macular edema had been enrolled. Although the sex ratio had not been mentioned in some studies, 140 of the cases were females in those mentioned. The age of patients enrolled in the selected studies varied from 38 to 96 years. The number of studied participants also varied from one patient in some case reports to 103 patients among the studies. In these studies, treatment duration varied from two days to 36 months. In a nunmber of studies, patients with sex-linked diabetic retinopathy with macular edema had been studied to evaluate the effects of Avastin on NPDR. Three of the studies were case reports in which the patients with NPDR, chronic macular edema, and vision loss had been treated with bevacizumab. Because the age, gender, and other informative demographic data had not been reported in some included articles, the data could not be categorized based on sex and age. Table 1 shows the general characteristics of studies included in this literature review.

Study results

The results showed that IVB injection in patients with diabetic macular edema increases acute visual acuity. Finding showed that intraoperative bevacizumab can improve the mean best corrected visual acuity (BCVA) from 0.80 at baseline to 0.54 at 6-months follow-up (12). Also results showed that mean central subfield thickness (CST) can increase from 316.02 μm to 339.56 μm after 6-months post treatment. Bevacizumab increased FAZ from 0.330 mm^2 at baseline to 0.434 mm^2 (14). Results of studies also showed that optical disc swelling and macular edema disappeared in three weeks after treatment with bevacizumab (17,18). In addition, results of other studies showed positive effects of IVB injection on the treatment of diabetic papillopathy (18,21). According to the reports, it was shown that treatment with bevacizumab increased FAZ and VA, while CMT reduced as a result of IVB injection (15). Findings of the included studies indicated that maximal reduction of VEGF level occurred seven days after IVB injection. Table 2 shows the main clinical outcomes of the treatment with Avastin.

Discussion

Since the clinical manifestations of NPDR stage in patients with diabetic retinopathy and macular edema are associated with increased vascular permeability, in particular, VEGF levels, therapeutic agents inhibiting VEGF may be used in the management of macular edema. Injection of IVB is considered as an effective VEGF inhibitor. It is also considered as a novel and effective therapy in the treatment of various ocular diseases such as retinal neovascularization, neovascular glaucoma, macular edema, and other ocular complications (22-24). Various studies have also demonstrated that IVB injection is a promising therapeutic agent in the management of patients with intraocular neovascular complication and macular edema (25). Previously, the safety and non-toxic effects of bevacizumab on human retinal pigment epithelium, pig choroidal endothelial cells, and rat retinal ganglions had been demonstrated (24,26). Toxicological assessment of the topical bevacizumab had also been shown no significant adverse effects on ocular epithelium and endothelium (27). As well, therapeutic potency of Avastin has been confirmed on iris rubeosis (28,29). Another study has shown that a single intravitreal ranibizumab (0.5 mg) injection

Table 1. General characteristics of the included articles.

No	Author Year Reference	Study design ®	Sex ratio	Country	Population	Number of patients
1	Gallego-Pinazo 2014 (12)	RS	27 female 32 male	Multicenter *	Diabetic patients who had cataract surgery and moderate-severe NPDR[1]	59
2	Nesmith 2014 (13)	CCS	61 female 42 male	USA	NPDR and AMD[2]	103
3	Feucht 2013 (14)	RS	31 female 22 male	Germany	Patients with macular edema and NPDR	53
4	Erol 2012 (15)	PS	19 female 10 male	Turkey	Diabetic macular edema	29
5	Davidović 2012 (16)	PiS	-	Serbia	Diabetic patients with NPDR	20
6	Al-Hinai 2011 (17)	CR	A 46 years old male	Oman	Macular edema and NPDR	1
7	Ornek 2010 (18)	CR	A 43 year old woman	Turkey	Mild NPDR	1
8	Lanzagorta-Aresti 2009 (19)	PiS	-	Spain	NPDR and macular edema	28
9	Chen 2009 (20)	CR	A 58 year old woman	USA	NPDR and chronic macular edema	1

® RS: Retrospective study, CCS: Case–control prospective study, PS: Prospective study, PiS: Pilot study, CR: Case-report, * Spain, Puerto Rico, Costa Rica, Brazil, Venezuela, Argentina, and Saudi Arabia. [1]NPDR: Nonproliferative diabetic retinopathy, [2]AMD: Age-related macular degeneration.

completely resolved the optic disc swelling with no need for additional treatment (21).

Comparison between the effects of IVB injection and panretinal photocoagulation (PRP) in the treatment of severe NPDR and PDR showed that central macular edema was significantly lower in patients treated with bevacizumab rather than PRP, but the final corrected VA was not significantly different in both groups (30). Findings showed that IVB injection increased VA and FAZ in patients with diabetic macular edema, while it reduced CMT following treatment (15,17).

Findings have shown that only 0.5 mg of ranibizumab and 1.25 mg of bevacizumab as intravitreal injection resulted in a decrease of the foveal thickness, and improved vision in patients with diabetic macular edema (31). In articles included in this literature review, the clinical effects of intravitreal injection of 1.25 mg bevacizumab has been examined in NPDR stage of diabetic retinopathy with macular edema in a certain time. The results showed that IVB injection could be safely used to treat various ocular disease, particularly NPDR stage of diabetic retinopathy with macular edema.

Conclusion

According to the results of included articles, IVB injection can be considered as a promising therapeutic strategy in the treatment of NPDR stage of diabetic retinopathy.

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Conflict of Interest

The authors declare no conflict of interest.

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Table 2. Variables and methods of assessment in the selected studies.

No	Author Reference	Variables *	Dose (mg/ml)	Mean follow-up	Method of assessment ®	Finding
1	Gallego-Pinazo (12)	BCVA, CST	1.25/0.05	6 months	OCT and FA	The use of bevacizumab at the time of cataract surgery in cases with pre-existent diabetic macular edema or NPDR[1].
2	Nesmith (13)	OSA	-	12 months	SQ	Result showed that poor responders to Avastin are at higher risk for OSA.
3	Feucht (14)	FAZ, BCVA	1.25/0.05	6-8 weeks	OCT and FA	The results confirmed the safety of IVB[2] injection in patients with macular edema due to NPDR and branch retinal vein occlusion.
4	Erol (15)	VA, CMT	1.25/0.05	3 months	OCT and FA	IVB injections can be used for chronic DME regardless of VA, CMT, or FAZ dimensions.
5	Davidović (16)	Serum levels of VEGF	1.25/0.05	1 month	FA and ELISA	IVB injections have an effect on decreasing systemic VEGF values.
6	Al-Hinai (17)	VA, optic disc	1.25/0.05	1 month	OCT, FA and FLP	Bevacizumab is a useful treatment in diabetic papillopathy.
7	Ornek (18)	VA, optic disc	1.25/0.05	3weeks	OCT and FA	IVB injection effectively treated diabetic papillopathy.
8	Lanzagorta-Aresti (19)	BCVA, CMT	-	36 months	OCT	IVB immediately after phacoemulsification prevents exacerbation of the macular edema.
9	Chen (20)	VA	-	2 days	OCT and FA	The use of IVB in chronic, refractory diabetic macular edema may cause acute visual acuity loss.

* BCVA: Best-corrected visual acuity, CST: Central subfield thickness, OSA: Obstructive sleep apnea, FAZ: Favela vascular zone, VA: Visual acuity, CMT: Central macular thickness, VEGF: Vascular endothelial growth factor, ®OCT: Optical coherence tomography, FA: Fluorescein angiography, SQ: Screening Questionnaire, FLP: Focallaser photocoagulation. [1]NPDR: Nonproliferative diabetic retinopathy, [2]IVB: Intravitreal bevacizumab.

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