Original Article

Mahidol University Journal of Pharmaceutical Sciences 2014; 41 (3), 23-30

# Safety of Intravitreal Bevacizumab Injection for Neovascular Age-Related Macular Degeneration and Diabetic Macular Edema: A Systematic Review

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## Abstract

Bevacizumab (IVB) has been widely used as an off-label treatment for treating neovascular age-related macular degeneration (nvAMD) and diabetic macular edema (DME) because its substantial lower cost than the approved drug named ranibizumab. However, there are concerns about possible serious adverse events (SAEs) of IVB particularly rare events and evidences supporting its safety profile remain inconclusive. This study aimed to examine serious ocular and systemic adverse events (AEs) of IVB in the treatments of nvAMD and DME. The articles were searched from Pubmed. Randomized controlled trials (RCTs), non-randomized studies, and prospective cohort studies, and case control study which reported SAEs of IVB compared with other anti-VEGF drugs in the treatment of nvAMD or DME were included. Studies which IVB were given in conjunction with other ocular procedures or therapies and articles published in non-English languages were excluded. Only 14 articles were included in this review. The incidences of endophthalmitis and arteriothrombotic events in nvAMD and DME patients were low. Although many studies concluded that the treatment with IVB was well-tolerated and had similar safety profile in patients with nvAMD and DME as comparing with IVR, pegaptanib, and different dosage regimen of IVB, this claim was opposed by a few studies. Large trials with longer follow up designed to detect particularly rare SAE are still required and it might be useful in treatment selection and decision making to allocate the resources for treatment of nvAMD and DME.

**Keyword:** Intravitreal injection, Bevacizumab, Neovascular age-related macular degeneration, Diabetic macular edema, Adverse events

## INTRODUCTION

New abnormal ocular blood vessels and their leakage of blood and fluid lead to vision loss and legal blindness in patients with neovascular age-related macular degeneration (nvAMD) and diabetic macular edema (DME)[1-6]. The most commonly used vascular endothelial growth factors (VEGF) inhibitors for counteracting the macular diseases involved with neovascularization are bevacizumab (Avastin®) and ranibizumab (Lucentis®). Ophthalmologists have prescribed bevacizumab which was primarily licensed for metastatic colorectal cancer (mCRC) to treat patients with nvAMD by intravitreal injection (IVT) as an off-label treatment since 2005. They revealed that IVT administration of bevacizumab can significantly reduce macular edema and improve visual acuity in the patients[3].

Although ranibizumab has been approved for the treatments of nvAMD, macular edema from retinal vein occlusion (RVO) and DME, it is very expensive and many patients worldwide have been unable to afford this medicine. Bevacizumab has

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been divided into small single-dose, prefilled syringes for intravitreal use by compounding pharmacies and extensively prescribed for treating these macular diseases in many countries due to the substantial lower cost of a single dose of bevacizumab in comparison to the cost of ranibizumab[3]. In addition, several studies has demonstrated the equivalent efficacy of bevacizumab and ranibizumab in patients with bevacizumab AMD and DME [2, 7-9]. However, the evidence supporting safety profile of bevacizumab are still insufficient. Therefore, this systematic review was conducted in order to identify serious ocular and systemic adverse events (AEs) of standard dose of intravitreal bevacizumab injection (IVB) in the treatments of nvAMD and DME when comparing with other anti-VEGF therapy.

## MATERIALS AND METHODS

### *Literature search*

A systematic search of Pubmed was conducted. Studies published through February 2013 were identified using the following search terms ((((“bevacizumab” [Supplementary Concept])) AND ((“Macular Degeneration”[Mesh]) OR “Macular Edema”[Mesh])). There was no manual search from the reference list of retrieved articles in this review.

### *Study selection and data extraction*

In this review, participants included the patients of any age and gender diagnosed with nvAMD or DME. The interested intervention in this study was IVB compared with other intravitreal anti-VEGF drugs including intravitreal ranibizumab injection (IVR). The outcomes of interest were serious ocular and systemic AEs particularly endophthalmitis, nonfatal myocardial infarction (MI), nonfatal stroke, and death from a vascular or unknown. The study designs included in this review were randomized controlled trials (RCTs), non-randomized trials (RTs), prospective cohort studies, and case-control studies. Studies which IVB was given in conjunction with other ocular procedures or therapies or published in a non-English language were excluded. Additionally, case series, case report, systematic review, and meta-analysis were not included in this review. Relevant data extracted included characteristics of study, study population, and principle findings (adverse events). All eligible articles which are randomized trials were undergone methodological quality assessment using Jadad scoring and the article with a Jadad score less than 3 out of 5 were excluded due to low quality. The screening, selection of articles, data extraction, and quality assessment was performed by one author (SS).

**<u>Inclusion criteria</u> (PICOS)**
**Patient population (P):**
patients with nvAMD or DME
**Interventions or exposure (I):**
1.25 mg/0.05 ml of IVB
**Comparator group (C):**
other intravitreal anti-VEGF drugs
**Outcome or endpoint (O):**
safety outcome focusing on SAEs
**Study design chosen (S):**
RCT, non-RT, prospective cohort study, and case-control study

## RESULTS AND DISCUSSION

Figure 1 shows the systematic review process. The electronic literature search identified 338 citations. From these, 41 non-English articles were removed to yield 297 citations for screening on the basis of title and abstract. Upon the screening, 235 citations were excluded, and 62 potentially relevant articles were retrieved for full-text review but 7 citations were not available as full-text. Of the potentially relevant full-text articles, 41 records failed to meet the inclusion criteria. Finally, there were 14 records included in this review and their study characteristics were presented in Table 1.

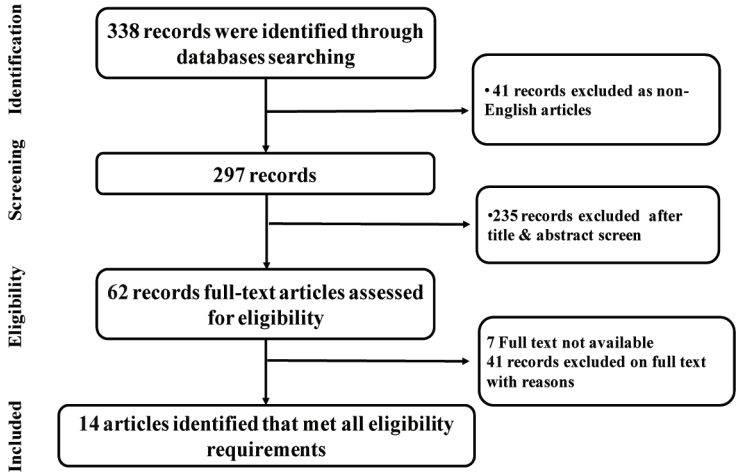


**Figure 1.** The systematic review process

There were 13 randomized trials [2, 7, 8, 10-19] and one case-control study[20]. All of the randomized trials had Jadad score greater or equal to 3. Among these eligible articles, the twelve (85.71%) studies examined the drug outcomes in patients with nvAMD whereas only 2 studies conducted in DME patients. IVB-treated groups were compared with IVR and pegaptanib (Macugen®) in 7 and 2 studies respectively. Certain SAEs of interested were extracted from the articles because of considerable concerns about rare serious systemic AEs such as arterial thromboembolic events (ATE) which were reported when administering bevacizumab at higher doses by intravenous injection for cancer therapy. Moreover, bevacizumab preparation and storage might increase risk of microbial contamination and cause a serious ocular infection called endophthalmitis.

**Table 1.** Study characteristics

| Study | Country | Population (patients) | Intervention(patients/eyes) | Comparator(patients/eyes) | Study design | Study period |
|---|---|---|---|---|---|---|
| **Chakravathy *et al (IVAN)* (2012)** [8] | UK | nAMD (628) (randomized to continuous and discontinuous treatments after the first 3 injections) | 1.25 mg IVB;n=305/305 eyes | 0.5 mg IVR;n=323/323 eyes | multicenter, factorial, noninferiority, randomized trial | 1 year (total: 2 years) |
| **Costa *et al* (2006)** [18] | Brazil | nvAMD | IVB 1 mg; n=15/15 eyes | IVB 1.5 mg; n=15/15 eyes<br>IVB 2 mg; n=15/15 eyes | prospective, nonrandomized, open-label trial (phase I) | 12 weeks |
| **French *et al* (2011)** [20] | US | nvAMD (exposure 3,021) | IVB only;n=1,302 IVR only;n=1,719 | anti-VEGF free dry AMD patients;n=117,364 | case-control study | 12 months |
| **Krebs *et al* (2013)** [10] | Austria | nvAMD (317) | IVB 1.25 mg; n=154/154 eyes | IVR0.5 mg; n=163/163 eyes | prospective, randomised, double masked, parallel group study | 12 months |
| **Lam *et al* (2009)** [17] | Hong Kong | DME (52) | IVB 1.25mg; n=26/26 eyes | IVB 2.5mg; n=26/26 eyes | 2-arm RCT | 6 months |
| **Li *et al* (2012)** [11] | China | nvAMD (185) | IVB 1.25 mg q 6 weeks x 8 injections n=91/91 eyes | IVB 1.25 mg q 6 weeks x 3 injections, then q 12 weeks x 2 injections; n=94/94 eyes | prospective,multicenter, open-label RCT | 48 weeks |
| **Martin *et al (CATT)* (2011)** [2] | US | nAMD/1208 patients | 1.25 mg IVB | 0.5 mg IVR | multicenter, single-blind, noninferiority RCT | 1 year (total: 2 years) |

**Table 1.** Study characteristics (continued)

| Study | Country | Population (patients) | Intervention(patients/eyes) | Comparator(patients/eyes) | Study design | Study period |
|---|---|---|---|---|---|---|
| **Martin *et al* *(CATT)* (2012)** [7] | US | nAMD/1208 patients | 1.25 mg IVB | 0.5 mg IVR | multicenter, single-blind, noninferiority RCT | 2 years |
| **Modarres *et al* (2009)** [16] | Iran | nvAMD (86) | IVB 1.25mg; n=47/47 eyes | IVB 2.5mg; n=39/39 eyes | prospective,randomized, comparative clinical trial | 5 months |
| **Schmid-Kubista *et al* (2011)** [12] | Austria | nvAMD (48) | *arm 1; n=13/13 eyes | *arm 2, n=18/18 eyes | prospective, masked, randomized, monocentric, pilot-study | 6 months |
| **Scott *et al* (2007)** [19] | US | DME (109) | **arm 2n=22/22 eyes | **arm 3, n=24/24 eyes; arm 4,n=22/22 eyes | phase 2 randomized, multi-center clinical trial | 24 weeks |
| **Subramanian *et al* (2009)** [15] | US | nvAMD (20) | IVB 1.25mg; n=13/13 eyes | IVR0.5 mg; n=7/7 eyes | Prospective, double-masked, randomized clinical trial | 6 months |
| **Subramanian *et al* (2010)** [14] | US | nvAMD (22) | IVB 1.25mg; n=15/15 eyes | IVR0.5 mg; n=7/7 eyes | Prospective, double-masked, randomized clinical trial | 12 months |
| **Tufail *et al* (2010)** [13] | UK | nvAMD (131) | IVB 1.25 mg; n=65 | Standard treatment (pegaptanib sodium 0.3 mg or PDT, sham); n=66 | Prospective, double masked, multicentre, RCT | 54 weeks |

*DME = diabetic macular edema; IVB = intravitreal bevacizumab injection; IVR = intravitreal ranibizumab injection; nvAMD = neovascular age-related macular degeneration; RT = randomized trial; RVO = retinal vein occlusion; UK = United Kingdom; US = United States*

* arm 1: 1.25-mg IVB q 6 weeks arm 2: 0.3-mg pegaptanib q 6 weeks arm 3: IVB 1 injection, then pegaptanib 2 injections q 6 weeks

** arm 1: focal photocoagulation at baseline, arm 2: 1.25-mg IVB at baseline and 6 weeks, arm 3: 2.5-mg IVB at baseline and 6 weeks, arm 4: 1.25-mg IVB at baseline and sham injection at 6 weeks, arm 5: 1.25-mg IVB at baseline, focal photocoagulation at 3 weeks, and 1.25-mg IVB at 6 weeks

Table 2 demonstrates the main findings of the systematic review. Regarding ocular AEs, majority of the studies reported only minor and transient the local AEs which their rates were not statistically significant different between the treatment groups. Many ocular AEs related to injection procedure such as subconjunctival hemorrhage, inflammation, vitreous hemorrhage, and elevated intraocular pressure (IOP) [11, 13-16, 18]. It should be noted that IOP elevation can occur in any case that give fluid into the vitreous cavity by intravitreal therapy and only sustained IOP elevation would be considered as an AE. The occurrence of endophthalmitis was found in studies of Martin *et al* [2, 7] and Scott *et al* [19] at the rate of less than 2% and there was no difference between treatment groups. Other serious ocular AEs such as severe uveitis, traumatic cataract, and retinal detachment (RD) were found at low rate [2, 8, 13].

**Table 2.** The main findings

| Particular SAEs of interest | Chakravathy (2012) [8] | Costa (2006) [18] | French (2011) [20] | Krebs (2013) [10] | Lam (2009) [17] | Li (2012) [11] | Martin (2011) [2] |
|---|---|---|---|---|---|---|---|
| **Ocular AEs** | | | | | | | |
| Serious ocular AEs | severe uveitis n=1; traumatic cataract n=1; retinal pigment epithelial tears n=3 | None | n/a | None | None | None | ENDOPHTHALMITIS: IVB 0.07% of injections in 586 patients vs. IVR 0.04% of injections in 599 patients (p=0.49) Other SAEs: < 1% of patients |
| **Systemic AEs** | no difference in serious systemic AEs between drugs (OR, 1.35; 95%CI, 0.80-2.27; p=0.25); ≥1 SAEs 12.5% vs. 9.6% (p=0.25) | None | n/a | 12.3% vs. 9.2% (p=0.37) (Severe vascular disorders 3.2% vs. 1.9%) | No significant SAE; 1 patients treated with 1.25-IVB amputated for foot gangrene from worsening diabetic neuropathy (unrelated to the study drug) | 4.4% vs. 1.1% (p=0.206) | ≥ 1 SAEs IVB-monthly 22.4% vs. IVR-monthly 17.6% vs. IVB-as needed 25.7% vs. IVR-as needed 20.5% (p=0.11); adjusted RR for IVB as compared with IVR = 1.29 (95%CI, 1.01-1.66; p=0.04) |
| cerebrovascular events | nonfatal stroke 0% vs. 1%; TIA 0.3% vs. 0.3% | None | n/a | stroke 0.65% vs. 0.61% (p=0.94) | None | None | ATE were similar among the 4 groups at 2-3% (p=0.97); VTE approx. 1% in all groups (p=0.08), 1.4% in IVB-monthly |
| cardiovascular events | ATE or HF 0.7% vs. 2.9%; OR, 0.23; | None | n/a | heart attack 1.95% vs. 1.23% (p=0.61) | None | None | |
| thromboembolic events | 95%CI, 0.05-1.07; p=0.03) but no | None | n/a | n/a | None | None | |
| **Death** | 1.7% vs. 1.9% (p=0.81) | None | adjusted OR* for all-cause mortality IVB 0.94 vs. IVR 0.85 (95%CI, 0.67-1.08) | 1.95% vs. 1.23% (p=0.61) | None | None | IVB-monthly 1.4% vs. IVR-monthly 1.3% vs. IVB-as needed 3.7% vs. IVR-as needed 1.7% (p=0.18) |
| **Remark** | ATE or HF found in IVR group more often than IVB group (p=0.03) but no difference between treatment regimens | only single dose and short-term follow up in a small group of patients | *the death hazard ratios were adjusted for age, gender, ocular and medical comorbidities (unadjusted: IVB 0.86 vs. IVR 0.88; 95%CI, 0.69-1.11) | small sample size (not powered to determine AEs of statistical significance) | | | rate of death, MI, and stroke in each group were similar (p>0.20); serious systemic AEs 24.1% vs. 19.0% (RR, 1.29;95%CI, 1.01-1.66) |
| **Ocular AEs** | | | | | | | |
| Serious ocular AEs | ENDOPHTHALMITIS: IVB 1.2% vs. IVR 0.7% (p=0.38) (10 of 11 cases found in monthly treated patients) | None | None | ENDOPHTHALMITIS: one patient treated with IVB (1 in 185 injections) | None | None | uveitis: 3% vs. 0% rhagmatogenous RD: 0% vs. 3% VH: 2% vs. 0% |
| **Systemic AEs** | ≥ 1 SAEs IVB 39.9% vs. IVR 31.7% (p=0.004); adjusted RR for IVB as compared with IVR = 1.30 (95%CI, 1.07-1.57; p=0.009) and as-needed group had higher rates than the monthly group RR=1.20 (95%CI, 0.98-1.47; p=0.08); GI disorders in IVB 4.8% vs. IVR 1.8% (p=0.005) | None | None | elevated of BP n=3; worsened renal function n=3 | None | None | non-ocular hemorrhage 0% vs. 1% |
| cerebrovascular events | ATE were similar: IVB 5% vs. IVR 4.7% | None | None | None | None | None | None |
| cardiovascular events | (p=0.89) (p=0.97); VTE: IVB 1.7% vs. | None | None | MI n=2 CHF n=1 | None | None | MI 1.5% vs. 0% |
| thromboembolic events | IVR 0.5% (p=0.054) | None | None | None | None | None | None |
| **Death** | IVB 6.1% vs. IVR 5.3% (p=0.62) | None | None | 1 subject died from pancreatic cancer in arm 2 | None | None | vascular death 1.5% vs. 0% |
| **Remark** | rate of death, MI, and stroke in each group were similar (p>0.60) | small sample size with short follow-up | | small sample size with short follow-up | This is an early result (only 6-month follow up); small sample size and majority of them are male-Caucacian patients | small sample size and majority of them are male-Caucacian patients | no imbalance in AEs between the groups |

*AE=adverse event; ATE=arteriothrombotic event; BP=blood pressure; CI=confident interval; CHF=congestive heart failure; HF=heart failure; IOP=intraocular pressure; MI=myocardial infarction; OR=odds raio; RD=retinal detachment; RR=risk ratio; SAE= serious adverse events; TIA=transient ischemic attack; VH=vitreous hemorrhage;VTE=venous thrombotic event*

In terms of systemic serious AEs of interest, the serious systemic AEs were found in IVB treated nvAMD and DME patients at low rates and not significantly different from IVR or pegaptanib injected groups in the majority of these studies, however Chakravathy and colleagues[8] reported that ATE or heart failure (HF) occurred in the IVR-treated group at greater rate than the IVB-treated group (OR, 0.23; 95%CI, 0.05-1.07; p=0.03) but no difference between continuous and discontinuous regimens. The studies by Martin *et al* [2, 7] suggested that IVB-treated group had higher rate of SAE (≥1 type) including gastrointestinal (GI) disorders than the compared group. The events more frequently found in as needed regimen than monthly regimen. Moreover, the rates of death, myocardial infarction (MI), and stroke were indifferent among the treatment groups. Other systemic AEs occurred in the eligible articles were non-ocular hemorrhage[13], GI disorder[7], worsened renal function[19], and elevated blood pressure[19]. The rate of all cause mortality between the arms (1.25 mg IVB vs. IVR/ pegaptanib) in these studies was similar. One study indicated that mild AEs were found more often in 2.5 mg IVB-treated group comparing to the standard dose of IVB (1.25 mg)[16].

The finding derived from certain studies should be interpreted with caution. Some studies suggested the limitation due to their relative small sample size and short-term of follow up period [10, 14-16, 18, 19]. This issue was also mentioned by Schmucker *et al* which highlighted methodological limitations of many studies especially insufficient sample size to detect rare SAEs of IVB and improper monitoring procedure for AEs [21]. Additionally, it was suggested that certain ATEs might be caused by either IVB or multiple cardiovascular risk factors in patients with nvAMD who are elderly [22]. Three DME cases threatened by fatal MI, CHF, and non-fatal MI after 1.25 mg or 2.5 mg IVB treatment had medical histories related to such events[19]. Martin et al found a higher the proportion of patients with SAEs in IVB group, however it was difficult to determine the cause-effect relationship as these excess SAEs widely distributed in disease categories not identified in previous studies as areas of concern [2]. Therefore, it cannot be concluded that IVB in the treatment of these macular diseases is as safe as IVR therapy. The more safety studies with high-quality are required. Due to ethical dilemma to conduct large RCT (head-to-head) comparing IVR and IVB, prospective observational study might be a good alternative study design and result derived from this kind of studies can be generalized to a broader context.

This review has two limitations. First, only one database was used for literature search. Other useful databases suggested for detecting safety signals such as other postmarketing surveillance databases (e.g. VigiBase™ of the Uppsala Monitoring Centre (UMC) which contains international drug safety data should be included. Second, this review excluded non-English papers, gray literature, and articles that could not be retrieved their full-text might, consequently, it might lead to potential publication bias.

## CONCLUSION

Based on available data, most of studies concluded that IVB and IVR have similar safety profile in nvAMD and DME patients. Although similar risk of ATEs between the treatment groups were found in several studies, a few studies revealed higher rate SAE in IVB treated groups. It was proposed that the longer follow-up and larger sample size may alter the result. It might not be appropriate to conclude that IVB is not associated with these AEs due to several reasons such as confounding factors (e.g. age, ocular and medical comorbidities, and socioeconomic status), intravitreal injection related complications (e.g. infection, VH, RD). Further studies should consider about time to events, the number and interval of injections as they might affect results.

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