

The Use of Intravitreal Anti-Vascular Endothelial Growth Factor Injection and Its Complications in Chiang Mai University Hospital

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Objective: To report the use of intravitreal (IVT) injections of anti-vascular endothelial growth factor agents (anti-VEGF) and its complications.

Material and Method: The authors performed a retrospective review of consecutive patients treated with IVT injection of anti-VEGF between May 2006 and December 2010 at Chiang Mai University Hospital. Demographic data and complications were registered.

Results: The present study included 1,006 eyes of 878 patients. Mean age was 60 years (range 1 month to 91 years). Mean follow-up time was 12 months (range 1 month to 54 months). Total injections were 2,077 given as 47, 210, 399, 575, and 846 injection per year between 2006 and 2010, respectively. Anti-VEGF agents were bevacizumab (1,878; 90.42%), ranibizumab (190; 9.15%), and pegaptanib (9; 0.43%). Indications for injection based on primary diagnosis were neovascular macular degeneration (38.5%), diabetic retinopathy (38%), and retinal vein occlusion (15.9%). The incidence of endophthalmitis was 0.048% (1/2,077) for all injections and 0.053% (1/1878) for bevacizumab.

Conclusion: The use of IVT injections of anti-VEGF is increasing, especially the use of bevacizumab. Incidence of ocular and systemic complications after IVT injection of anti-VEGF was low with no significant difference among the three anti-VEGFs agents.

Keywords: Intravitreal anti-vascular endothelial growth factor injection, Bevacizumab, Ranibizumab, Pegaptanib, Complication

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The use of intravitreal (IVT) injection of anti-vascular endothelial growth factor (VEGF) is rapidly increasing for various conditions, especially in ocular neovascular diseases such as neovascular age-related macular degeneration, proliferative diabetic retinopathy, diabetic macular edema, retinal vein occlusion, neovascular glaucoma, and retinopathy of prematurity⁽¹⁻⁵⁾. There are three available anti-VEGF agents for intravitreal treatment. The first is pegaptanib sodium (Macugen, Eyetech Pharmaceuticals; Inc., New York, NY, and Pfizer Inc., New York, NY). It is an aptamer and selectively binds to VEGF₁₆₅. Another is ranibizumab (Lucentis, Genentech; Inc., South San Francisco, CA; co-developed by Genentech, Inc., and

Novartis), an antibody fragment. Finally, there is bevacizumab (Avastin; Genentech, Inc., San Francisco, CA), a recombinant humanized monoclonal antibody. The last two interact with all isoforms of VEGF-A.

The safety of each anti-VEGF agent is different due to the different isoform-binding specificities⁽⁶⁾. To determine the complications and the use of IVT anti-VEGF injection, we reviewed the medical records of patients undergoing IVT anti-VEGF injections at our institution.

Material and Method

A retrospective review of consecutive patients treated with IVT injection of anti-VEGF agents (including bevacizumab, ranibizumab, and pegaptanib) was performed between May 2006 and December 2010 at Chiang Mai University Hospital. Demographic data including age, sex, follow-up time, indication for injection, number of injections and the ocular/systemic complications were registered.

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The clinical indications for injections included neovascular macular degeneration (age-related macular degeneration, polypoidal choroidovasculopathy and retinal angiomatous proliferation), diabetic retinopathy (proliferative diabetic retinopathy and clinically significant macular edema), retinal vein occlusion (central and branch retinal vein occlusion), uveitis (uveitis and vasculitis), cystoid macular edema (cystoid macular edema, parafoveal telangiectasia and radiation retinopathy), neovascular glaucoma, retinopathy of prematurity, other choroidal neovascularization (angioid streak and myopic) and others (Coats's disease and exudative retinal detachment).

All patients were informed in detail since this is an off-label use of the bevacizumab; consent was obtained for each agent before the injection. Patients were pre-treated with 4% lidocaine drops. All injections were performed following the standard protocol for IVT injection in the operating room. This consisted of 5% povidone-iodine onto conjunctiva and 10% povidone-iodine scrub on the eyelid and lashes. A sterile drape was placed and sterile wire lid speculum was inserted. Each patient received either 1.25 mg/0.05 ml of bevacizumab, 0.5 mg/0.05 ml ranibizumab, or 0.3 mg/0.05 ml pegaptanib IVT injection at inferotemporal quadrant through pars plana in each eye by a second or third year residents wearing sterile gloves and masks. Eyes were irrigated with 0.9% normal saline and Terramycin eye ointment applied at the end of procedure. Post-injection, patients were instructed to use the topical tobramycin four times a day for one week. None had received topical antibiotics before the day of injection. Regarding to the follow-up protocol, all patients were re-evaluated one week later. Patients were informed to visit earlier if any unusual signs or symptoms occurred.

The preparation of bevacizumab was done by the hospital pharmacist by dividing 4 ml of bevacizumab (25 mg/ml, Genentech/Roche) into 60 to 70 ready-to-use syringes of 1.25 mg/0.05 ml each in a sterile hood and stored at -80 degrees Celsius.

Descriptive statistics were used to summary the reports by a software package, SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). The present study was approved by a suitably constituted Ethics Committee of the institution within which the work was undertaken and conformed to the provisions of the Declaration of Helsinki.

Results

The present study included 1,006 eyes of 878 patients (433 males and 445 females). Mean age was 60 years (median 60 years, range 1 month to 91 years). Mean follow-up time was 12 months (median 7 months, range 1 month to 54 months). The total injections were 2,077 injections, including bevacizumab 1,878 (90.42%), ranibizumab 190 (9.15%), and pegaptanib 9 (0.43%). The distribution of the number of injection per year is shown in Fig. 1. Indications for injection based on primary diagnosis were neovascular macular degeneration 38.5%, diabetic retinopathy 38%, retinal vein occlusion 15.9%, and other 7.6% (Fig. 2). Most of our patients (59.1%) received one injection while only 1.5% received more than ten injections.

The average number of injections per eye was 2.06 (median 1, range 1-20). Patients with neovascular macular degeneration had highest number of injections per eye (mean 2.95, median 2, range 1-20) followed by choroidal neovascularization from angioid streak/high myopia (mean 2.67,

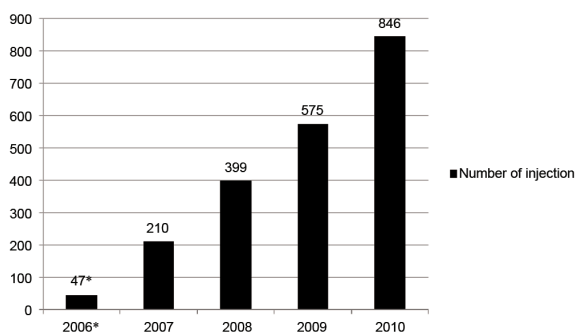


Fig. 1 The distribution of the number of injection per year. * May 2006 to December 2006

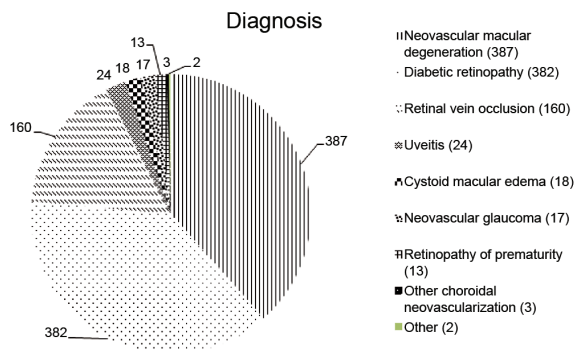


Fig. 2 Indications for injection based on primary diagnosis (number of eye).

median 3, range 1-4) and retinal vein occlusion (mean 2.15, median 1, range 1-15).

The average number of injections per eye per year was 2.12. Patients with neovascular macular degeneration had highest number of injections per eye per year (2.87) followed by retinal vein occlusion (2.39 injections per eye per year) and choroidal neovascularization from angioid streak/high myopia (2.09 injections per eye per year).

Regarding the incidence of complications, only one patient developed endophthalmitis after the seventh bevacizumab injection. Therefore, the incidence rate of endophthalmitis was 0.048% (1/2,077) for total number of injections and 0.053% after bevacizumab injections. However, the authors did not find any evidence of glaucoma, retinal detachment, traumatic cataract, severe uveitis, retinal pigment epithelium tear, stroke, or death.

The endophthalmitis case was a 66-year-old woman diagnosed with neovascular age-related macular degeneration in her right eye who had been treated with IVT bevacizumab injection. She had an approximately 6 disc diameter macular lesion. The initial visual acuity was counting fingers but she insisted on treatment. On the first day after the seventh bevacizumab injection, she developed eye pain and redness but did not come to the hospital. One week later, she returned to the hospital with complaint of decreased vision and severe eye pain. On eye examination, the visual acuity in the right eye was hand motion. There was hypopyon in the anterior chamber with vitreous opacity 4+. B-scan echography found vitreous opacity without retinal/choroidal detachment. Post injection endophthalmitis was diagnosed. IVT tap for culture and injection with ceftazidime 2.25 mg/0.1 ml and vancomycin 1 mg/0.1 ml were performed. Additionally, topical cefazolin (33 mg/ml) and gentamicin (14 mg/ml) every 2 hour were administered. Two days later, her clinical examination slightly improved (no hypopyon but still vitreous opacity 4+). Vitreous culture was positive for *Staphylococcus aureus* sensitive to vancomycin. Therefore, IVT vancomycin 1 mg/0.1 ml was re-injected. Over the next two days, her visual acuity decreased to light projection then 23-gauge pars plana vitrectomy and IVT vancomycin 1 mg/0.1 ml was performed (on post bevacizumab injection day 11). Inflammation subsided, no vitreous cells were present and her vision became hand motion. Unfortunately, 6-month later, the eye developed phthisis.

Discussion

IVT anti-VEGF agents are being widely used due to their efficacy in the treatment of ocular neovascular diseases; no obvious evidence of retinal toxicity has been reported. Each anti-VEGF agent has its isoform-binding specificities resulting in differences in efficacy and safety⁽⁶⁾.

Pegaptanib is selective VEGF isoform inhibition. It binds VEGF₁₆₅ with high specificity and affinity because VEGF₁₆₅ is the predominant isoform that contributes to pathologic ocular neovascularization and vascular permeability^(7,8). However, from clinical experience pegaptanib can slow down the rate of vision loss but does not restore vision by any statistically significant amount. Both ranibizumab and bevacizumab, potent inhibitors of all VEGF isoforms with similar target specificity⁽⁹⁻¹¹⁾, show better outcomes. Although ranibizumab has a higher affinity for VEGF (5 to 20 fold)⁽¹⁰⁾, several previous studies have found that bevacizumab associated with improvement in visual acuity⁽¹²⁻¹⁴⁾ and the efficacy of bevacizumab was not inferior to ranibizumab in the treatment of choroidal neovascularization secondary to age-related macular degeneration (AMD)⁽¹⁵⁻¹⁷⁾.

Nowadays, using bevacizumab is vastly popular because it is much less costly. Drug cost per-dose is approximately 2,000 US\$ for ranibizumab, 800 US\$ for pegaptanib and 50 US\$ for bevacizumab, which means that ranibizumab and pegaptanib are 40-fold and 16-fold higher in cost per dose when compared to bevacizumab. In our institute, the difference is even higher (90-fold and 40-fold). Raftery J et al⁽¹⁸⁾ demonstrated that ranibizumab had less cost-effectiveness compared to bevacizumab. With this cost, ranibizumab should be at least 2.5 times more efficacious. However, the ophthalmologists should not take only the cost of medication in consideration but we should also think about their adverse events. We have to deal with others costs such as the cost of dealing with adverse events or the cost of living with these adverse events.

From the randomized clinical trials of pegaptanib and ranibizumab and retrospective surveys of bevacizumab, all had low incidences of injection-related serious adverse events such as endophthalmitis, traumatic cataract, and retinal detachment as a result of standardized injection procedures^(9,11,19-26). The per-injection endophthalmitis rate of post-IVT anti-VEGF injections reported earlier were 0.014%-0.2% which is not different among the kinds of

anti-VEGF^(9,11,22,25-34). Our series had the similar rate (0.048%).

According to the ocular safety studies, the main ocular adverse event associated with ranibizumab were grades 3 or 4 ocular inflammation (2.1%-2.9%)^(9,11,24). Severe uveitis is a common ocular adverse event of bevacizumab (0.09%-0.4%)^(26,35). Pegaptanib had no reported ocular problems⁽³⁶⁾. Nevertheless, in most cases, ocular inflammation subsided with or without medication. In our series, none had more than grade 1 anterior chamber reaction.

Another important concern is the systemic safety. Though we use lower doses of anti-VEGF for IVT than for intravenous administration, patients with ocular neovascular diseases may have blood-retinal barrier breakdown that can increase the rate of ocular clearance through the systemic circulation and lead to greater systemic exposure^(37,38). Among these three agents, bevacizumab can have a longer systemic exposure because it has broad range of plasma concentration (pegaptanib 6-7 ng/mL⁽³⁶⁾, ranibizumab 0.79-2.9 ng/mL⁽³⁹⁾, bevacizumab 20-687 ng/mL; Csaky et al IOVS 2007; 48: ARVO E-Abstract 4936) and has the longest systemic half-life (pegaptanib 10 days⁽³⁶⁾, ranibizumab 0.1 day⁽³⁹⁾, bevacizumab 12.3 days⁽⁴⁰⁾). In addition, pegaptanib is a selective VEGF₁₆₅ isoform inhibition^(7,8,41) and ranibizumab is an antibody-binding fragment that has no domain necessary to activate complement-mediated cytotoxicity or to interact with Fc receptors on immune cells⁽¹⁰⁾. From these data, it is prudent to provide systemic monitoring especially in the patients receiving IVT bevacizumab injection.

The clinical trials of pegaptanib showed no systemic adverse events, but these trials excluded the patients with history of severe heart diseases or myocardial infarctions within six months or stroke within 12 months^(20,21).

In ranibizumab trials, the overall incidence of systemic adverse events was small but increase in non-ocular hemorrhages^(9,11,24) and thromboembolic events⁽⁴²⁾. Using combined data from ANCHOR and MARINA trials, Gillies et al⁽⁴³⁾ indicated that there was a significant increase in the occurrence of non-ocular hemorrhage in ranibizumab group (7.8% vs. 4.2% control group). From meta-analysis of ranibizumab trials, Ueta et al⁽⁴⁴⁾ showed that there was a significant increased incidence of cardiovascular accidents including strokes, transient ischemic attacks or cerebral ischemic incidents (2.2% vs. 0.7% sham group) but found no association with myocardial infarction.

There were substantial data concerning the systemic safety of bevacizumab from uncontrolled sources and the results were varied^(25,26,45). The frequent systemic adverse events included increase blood pressure (0.21-0.59%), cerebrovascular accidents (0.07-0.5%), deep venous thromboses (0.01%), myocardial infarction (0.4%), iliac artery aneurysms (0.17%) and death (0.04-0.43%)^(25,26). Comparison of AMD Treatments Trials (CATT), a clinical trial to compare the effects of ranibizumab and bevacizumab in patients with neovascular AMD, raised concerns that bevacizumab was not as safe as ranibizumab. Although there were no differences between the drugs in rates of death, arteriothrombotic events and venous thrombotic events, there were more systemic serious adverse events in patients treated with bevacizumab (risk ratio 1.30)^(16,17). None of our patients had a stroke or died. However, the complication rate may increase when the injections are repeatedly applied; therefore, close monitoring should be considered especially with multiple IVT bevacizumab injections.

The drawback in the present study was its retrospective character; reviewing medical records retrospectively may result in the loss of some data. In addition, systemic complications could be underestimated if patients returned to hospitals other than our own. Further, ocular complications may be also underreported because the instruments that can detect minute inflammation, such as laser flare interferometer are not available in our institute. Because we re-evaluated the patients at one week, some ocular complications such as increased cell/flare or increased intraocular pressure may have disappeared by that time^(11,21,46-49).

Conclusion

The rates of serious ocular and systemic adverse events after IVT anti-VEGF injections were low and there was no significant difference among three anti-VEGFs agents. To reduce adverse events, the ophthalmologists should select the appropriate cases, follow the standard protocol for IVT injection, and monitor regularly.

What is already known on this topic?

Intravitreal anti-vascular endothelial growth factor agents are being widely used in the treatment of ocular neovascular disease especially bevacizumab because it is much less costly. Previous studies found that ranibizumab and bevacizumab had good efficacy.

In terms of safety, there are many reports to support ranibizumab but in the case of bevacizumab, it is still worrisome.

What this study adds?

In northern Thailand, the rates of serious ocular and systemic adverse events after intravitreal bevacizumab injections were low (0.053%, 0%, respectively). However, the ophthalmologists should use it cautiously.

Potential conflicts of interest

None.

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การใช้ *anti-vascular endothelial growth factor* โดยการฉีดเข้าวุ้นตาและภาวะแทรกซ้อนในผู้ป่วยที่มีโรคภัยโรครักษา โรงพยาบาลมหาวิทยาลัยเชียงใหม่

ภาวดี คุณภาวิศรุต, นิธิรัชต์ แสนเพ็ญ, นิมิตร อธิพันธ์กุล, ดิเรก ผาติกุลศิลา, เจนจิต ชูฒยากร, ณวัฒน์ วัฒนชัย, เกษรา พัฒนพิฑูรย์

จุดประสงค์: เพื่อศึกษาการใช้ *anti-vascular endothelial growth factor* โดยการฉีดเข้าวุ้นตา และภาวะแทรกซ้อนในผู้ป่วยที่มีโรคภัยโรครักษา โรงพยาบาลมหาวิทยาลัยเชียงใหม่

วัสดุและวิธีการ: การศึกษาย้อนหลังโดยเก็บรวบรวมข้อมูลผู้ป่วยที่ได้รับการฉีด *anti-vascular endothelial growth factor* เข้าวุ้นตาในช่วงเดือนพฤษภาคม พ.ศ. 2549 ถึง 31 ธันวาคม พ.ศ. 2553 ที่โรงพยาบาลมหาวิทยาลัยเชียงใหม่ โดยบันทึกข้อมูลทั่วไปและภาวะแทรกซ้อนที่เกิดขึ้น

ผลการศึกษา: ผู้ป่วยทั้งหมดที่ได้รับการฉีด *anti-vascular endothelial growth factor* เข้าวุ้นตาจำนวน 878 ราย (1,006 ตา) แยกเป็นผู้ชาย 433 ราย ผู้หญิง 445 ราย อายุเฉลี่ย 60 ปี (อยู่ในช่วงอายุ 1 เดือน ถึง 90 ปี) ระยะเวลาเฉลี่ยในการติดตามการรักษา 12 เดือน (อยู่ในช่วงเวลา 1 เดือน ถึง 54 เดือน) จำนวนการฉีดยาทั้งหมด 2,077 ครั้ง โดยจำนวนครั้งในการฉีดแต่ละปี พ.ศ. 2549 จำนวน 47 ครั้ง พ.ศ. 2550 จำนวน 210 ครั้ง พ.ศ. 2551 จำนวน 399 ครั้ง พ.ศ. 2552 จำนวน 575 ครั้ง และ พ.ศ. 2553 จำนวน 846 ครั้ง โดย *anti-vascular endothelial growth factor* ที่ใช้ในการฉีดเข้าวุ้นตาแบ่งเป็น *bevacizumab* (1,878 ครั้ง; ร้อยละ 90.42) *ranibizumab* (190 ครั้ง; ร้อยละ 9.15) *pegaptanib* (9 ครั้ง; ร้อยละ 0.43) ข้อบ่งชี้ในการฉีดยาตามการวินิจฉัยเบื้องต้น แบ่งได้เป็นกลุ่ม *neovascular macular degeneration* ร้อยละ 38.5 กลุ่ม *diabetic retinopathy* ร้อยละ 38 กลุ่ม *retinal vein occlusion* ร้อยละ 15.9 และกลุ่มโรคอื่นๆ ร้อยละ 7.6 อุบัติการณ์การเกิด *endophthalmitis* คิดเป็นร้อยละ 0.048 จากจำนวนการฉีด *anti-vascular endothelial growth factor* ทั้งหมดและคิดเป็นร้อยละ 0.053 จากจำนวนการฉีด *bevacizumab*

สรุป: แนวโน้มการฉีด *anti-vascular endothelial growth factor* เข้าวุ้นตานี้มีแนวโน้มที่เพิ่มมากขึ้น โดยเฉพาะด้วย *bevacizumab* และอุบัติการณ์การเกิด *endophthalmitis* หลังจากการฉีด *anti-vascular endothelial growth factor* เข้าวุ้นตานี้เกิดขึ้นน้อยมากและไม่พบว่ามีผลแตกต่างกันอย่างมีนัยสำคัญระหว่างยาทั้งสามชนิด
