Intravitreal Ranibizumab Treatment for Non-Proliferative Idiopathic Macular Telangiectasia

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Abstract

**Background:** Idiopathic macular telangiectasia (IMT) associates with incompetence and ectasia of parafoveal retinal capillaries, causing significant loss of central vision. Many treatment modalities have been proposed to improve visual acuity such as laser, intravitreal injection of steroid, and anti-vascular endothelial growth factors. Nevertheless, the improvement in visual acuity was inconsistent.

**Objective:** To evaluate the effect of intravitreal ranibizumab on non-proliferative stage of idiopathic macular telangiectasia (IMT) in Thailand.

**Methods:** We conducted a retrospective, case series of 10 eyes (10 patients) in non-proliferative IMT treated with monthly intravitreal injection of 0.5 mg ranibizumab between July 2012 to March 2014 at Ramathibodi Hospital. Ophthalmic examination data, including best-corrected visual acuity (BCVA), fundus photograph, optical coherence tomography (OCT) and fluorescein angiogram (FA) were collected and interpreted by an experienced retinal specialist.

**Results:** Mean age was 52.9 ± 9.7 years. Median follow up time was 12.0 (8.0 - 17.0) months. Median BCVA improved from 0.35 (0.2 - 0.4) Logarithm of the Minimum Angle of Resolution (LogMAR) at baseline to 0.10 (0.0 - 0.3) LogMAR and 0.10 (0.0 - 0.4) LogMAR at third month and last visit, respectively. Mean central retinal thickness (CRT) was 374.3 ± 105.3 µm at baseline and decreased to 257.4 ± 84.3 µm and 242.4 ± 88.3 µm at third month and last visit, respectively. Mean changes in BCVA and CRT showed statistical significant different at third months and last visit compared to baseline. FA showed the reduction of leakage and staining at the end of treatment compared to baseline. No systemic and ocular adverse events were found.

**Conclusions:** Intravitreal ranibizumab might be the promising treatment for non-proliferative stage of IMT, in term of improving BCVA, decreasing CRT and FA leakage.

**Keywords:** Idiopathic macular telangiectasia, Retinal telangiectasia, Ranibizumab, Vascular endothelial growth factor

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Introduction

Idiopathic juxtafoveolar retinal telangiectasia (IJRT) was first described by Gass in 1982 and was further classified by Gass and Blodi in 1993. In 2006, Yannuzzi et al. proposed a new simplified classification termed idiopathic macular telangiectasia (IMT) into 2 subtypes. Type 1 was defined as the unilateral aneurysmal telangiectasia and type 2 was defined as the bilateral perifoveal telangiectasia. The pathogenesis of IMT was still unknown and the abnormality associated with incompetence and ectasia of parafoveal retinal capillaries. IMT caused significant loss of central vision due to retinal atrophy, accumulation of fluid at intraretina or subretina, subretinal neovascularization and subretinal fibrosis.

Many treatments had been proposed for non-proliferative stage of IMT such as focal argon laser photocoagulation, photodynamic therapy (PDT) and intravitreal injection of triamcinolone that revealed no beneficial effect. In the other hand, the intravitreal anti-VEGFs were reported short term anatomical and functional improvement. Both of ranibizumab (0.3 and 0.5 mg) and bevacizumab (1.25 mg) with monthly monitoring showed reduction in retinal thickening and fluorescein leakage. Nevertheless, the improvement in visual acuity was inconsistent. The purpose of this study is to evaluate the effect of intravitreal ranibizumab for non-proliferative stage of idiopathic macular telangiectasia (IMT).

Materials and Methods

Ten eyes (10 patients; 9 males and 1 female) with non-proliferative IMT which had been treated with monthly injection of intravitreal ranibizumab between July 2012 to March 2014, were retrospectively reviewed at Department of Ophthalmology, Ramathibodi Hospital, Thailand. This study complied with the tenets of the Declaration of Helsinki. The study protocol was approved by the institutional review board and the ethics committee of Ramathibodi Hospital, Mahidol University.

All patients received complete ophthalmic examination, including measurements of best-corrected visual acuity (BCVA), slit lamp biomicroscopy, color fundus photograph, spectral-domain optical coherence tomography (OCT; Spectralis®, Heidelberg Engineering, Germany) and fluorescein angiogram (FA; HRA®, Heidelberg Engineering, Germany).

Diagnosis of IMT was based on fundus examination, FA and OCT (7 eyes were type 1 IMT and 3 eyes were type 2 IMT according to Yannuzzi et al.’s classification). We excluded other causes of neovascular maculopathy (neovascular age-related macular degeneration, idiopathic polypoidal choroidal vasculopathy), secondary macular telangiectasia (diabetic macular edema, retinal vein occlusion, radiation retinopathy).

Treatment was performed under sterile technique with topical anesthesia. Ranibizumab (0.5 mg/0.05 ml) was injected intravitreally through pars plana (3.5 - 4.0 mm posterior to limbus) with 30-gauge needle. All patients were re-examined for BCVA and OCT in 4 weeks after injection. Re-treatment was considered in case of: 1) Central retinal thickness (CRT) in OCT show no improvement (less than 100 µm reduction or increase in CRT or persist of subretinal fluid), 2) BCVA gain less than 5 letters. Discontinue of treatment would be considered if; 1) BCVA and OCT showed no improvement after 3 consecutive injections of ranibizumab, 2) OCT showed no subretinal fluid after intravitreal injections of ranibizumab.
Data were collected and interpreted by an experienced retinal specialist (W.P.) in every visit. Data were analyzed by using Stata software (StataCorp. Version 14. College Station, TX: StataCorp LP; 2015). Reported in term of mean and standard deviation if the data were normal distributions, and median and interquartile range if the data were non-normal distributions. The Hausman test and the random-effects linear regression model were used to determine the statistical significant changes of parameters at $P$-value < 0.05.

Results
Mean age was 52.9 ± 9.7 years. Median follow up time was 12.0 (8.0 - 17.0) months. Median duration of symptom before treatment was 52.5 (30 - 90) days. After the treatment, the median BCVA increased from 0.35 (0.2 - 0.4) Logarithm of the Minimum Angle of Resolution (LogMAR) at baseline to 0.25 (0.1 - 0.4) LogMAR, 0.10 (0.0 - 0.3) LogMAR and 0.10 (0.0 - 0.4) LogMAR at 1st, 3rd month and the last visit, respectively. Mean CRT was 374.3 ± 105.3 µm at baseline and decreased to 281.6 ± 101.4 µm, 257.4 ± 84.3 µm and 242.4 ± 88.3 µm at 1st, 3rd month and the last follow up period, respectively. (Table 1)

Of seven eyes with type 1 IMT, the microaneurysms decreased in 4 eyes (the microaneurysms disappeared from fundus photograph and FA in one eye) and remained stable in 3 eyes. In three eyes with type 2 IMT, macular edema decreased in 2 eyes while foveal atrophy (from OCT) developed in one eye. The decrease of microaneurysms, macular edema and subretinal fluid occurred after second or third injection in both groups.

The result of random-effects linear regression model of all eyes showed statistical significant differences of LogMAR BCVA and CRT at 1 month, 3 months and last visit compared to baseline (Table 2, 3). In subgroup analysis of both type 1 and type 2 IMT eyes also showed statistical significant changes of LogMAR BCVA and CRT measured by OCT at 3 months and last visit comparing to baseline.

FA showed the reduction of leakage and staining area after the end of treatment. Mean intravitreal injection was 3.3 ± 1.1 times with one-month interval. No systemic and ocular adverse event was found in this study.
Table 1  Summary of individual data, including clinical data, OCT and FA finding previous and after the treatment in 10 eyes of 10 IMT patients

<table>
<thead>
<tr>
<th>Case</th>
<th>IMT type</th>
<th>Duration of symptom (mo)</th>
<th>LogMAR BCVA</th>
<th>Fundus photograph</th>
<th>CRT in OCT (µm)</th>
<th>FA</th>
<th>No. of injection</th>
<th>Total F/U time (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0.3</td>
<td>0.0</td>
<td>MAs with SRF</td>
<td>MAs disappeared</td>
<td>398  219</td>
<td>Multiple hyperF spots with leakage</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.5</td>
<td>0.4</td>
<td>0.1</td>
<td>MAs present</td>
<td>MAs decreased in number</td>
<td>352  222</td>
<td>Multiple hyperF spots with leakage</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0.3</td>
<td>0.9</td>
<td>0.3</td>
<td>MAs with SRF</td>
<td>MAs decreased in number</td>
<td>232  177</td>
<td>Multiple hyperF spots with leakage</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>2</td>
<td>0.4</td>
<td>0.1</td>
<td>MAs</td>
<td>MAs decreased in number</td>
<td>465  182</td>
<td>Multiple hyperF spots with leakage</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1.5</td>
<td>0.4</td>
<td>0.4</td>
<td>MAs with SRF</td>
<td>Stable of MAs</td>
<td>400  297</td>
<td>Multiple hyperF spots with leakage</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>4</td>
<td>0.2</td>
<td>0.4</td>
<td>MAs with HE</td>
<td>Stable of MAs</td>
<td>533  447</td>
<td>Multiple hyperF spots with leakage</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>2</td>
<td>0.2</td>
<td>0.0</td>
<td>MAs with SRF</td>
<td>MAs decreased in number</td>
<td>509  318</td>
<td>Multiple hyperF spots with leakage</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>3</td>
<td>0.3</td>
<td>0.0</td>
<td>Telangiectasia at parafovea</td>
<td>Loss of retinal transparency</td>
<td>262  203</td>
<td>Late staining and leakage of telangiectasia</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>Telangiectasia at parafovea</td>
<td>Loss of retinal transparency</td>
<td>322  205</td>
<td>Late staining and leakage of telangiectasia</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>1</td>
<td>0.5</td>
<td>0.4</td>
<td>Telangiectasia at parafovea with SRF</td>
<td>Loss of retinal transparency and RPE abnormality</td>
<td>270  154</td>
<td>Late staining and leakage of telangiectasia</td>
</tr>
</tbody>
</table>

IMT idiopathic macular telangiectasia, BCVA best-corrected visual acuity (BCVA), OCT optical coherence tomography (OCT), FA fluorescein angiogram, CRT central retinal thickness, MAs microaneurysms, hyperF hyperfluorescent, SRF subretinal fluid, RPE retinal pigmented epithelium, HE hard exudate
Case 4: A 56 years-old Thai man presented with blurred vision and metamorphopsia in his left eye for 2 months. BCVA was 0.4 LogMAR. Fundus examination revealed parafoveal microaneurysms, retinal thickening and intraretinal exudation. OCT showed cystoid macular edema with hyperreflective dots in outer retina and FA showed aneurysmal telangiectasia with leakage which is typical for type 1 IMT. No abnormal finding was found in his right eye. Ranibizumab was injected 4 times at 4-week intervals. Three months after last injection, BCVA improved to 0.1 LogMAR, OCT showed reduction of cystoid macular edema and central retinal thickness reduced from 465 to 182 µm (Figure 1).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Change in LogMAR best-corrected visual acuity (BCVA) at 1 month, 3 months and last visit compare to baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 month</td>
</tr>
<tr>
<td>Mean change in LogMAR BCVA</td>
<td>95% CI</td>
</tr>
<tr>
<td>10 eyes</td>
<td>-0.12</td>
</tr>
<tr>
<td>Type 1 (7 eyes)</td>
<td>-0.11</td>
</tr>
<tr>
<td>Type 2 (3 eyes)</td>
<td>-0.13</td>
</tr>
</tbody>
</table>

* Statistical significant (P - value < 0.05)

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Change in central retinal thickness (CRT) at 1 month, 3 months and last visit compare to baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 month</td>
</tr>
<tr>
<td>Mean change in CRT (µm)</td>
<td>95% CI</td>
</tr>
<tr>
<td>10 eyes</td>
<td>-92.7</td>
</tr>
<tr>
<td>Type 1 (7 eyes)</td>
<td>-98.0</td>
</tr>
<tr>
<td>Type 2 (3 eyes)</td>
<td>-80.3</td>
</tr>
</tbody>
</table>

* Statistical significant (P - value < 0.05)
Case 6: A 58 years-old Thai man had metamorphopsia in his left eye for 4 months. BCVA was 0.2 LogMAR. Fundus examination showed microaneurysms, retinal thickening with marked intraretinal exudation. OCT showed cystoid macular edema and FA showed aneurysmal telangiectasia with leakage (Figure 2). Ranibizumab was injected 5 times at 4-week intervals. At ten months after last injection, BCVA reduced to 0.3 LogMAR, OCT showed reduction of cystoid macular edema and CRT reduced from 533 to 98 µm. Visual acuity decreased to 0.4 and the OCT showed slightly increased of cystoid macular edema and CRT was 447 µm at the final follow-up (21 months after last treatment).

Figure 1  
Case number 4, (a) fundus photography showed parafoveal microaneurysms, retinal thickening and intraretinal exudation. (b) Optical coherence tomography (OCT) showed cystoid macular edema with hyperreflective dots in outer retina, (c) fluorescein angiogram (FA) showed aneurysmal telangiectasia with leakage which is typical for type 1 idiopathic macular telangiectasia (IMT). Three months after last intravitreal injections of Anti-VEGF, (d) OCT showed reduction of cystoid macular edema and central retinal thickness reduced from 465 to 182 µm and (e) decreased of leakage in FA.
Discussion

To date, the etiology and pathogenesis of IMT is not clearly understood. The diagnosis is still difficult in early stage of the disease and there is no established treatment protocol for non-proliferative IMT. Anti-VEGF seems to have a role in treatment of macular edema from non-proliferative IMT type 1 and 2 by reduced abnormal hyperpermeability of capillary network. The improvement of vision is different among previous studies and the response is unpredictable.

In our case series, intravitreal injection of ranibizumab (0.5 mg) improved visual outcome in 8 eyes of IMT and reduced in both leakage on FA as well as CRT. The eyes with type 1 IMT showed significant improvement in functional and anatomical finding at 3 months and last visit. Although the eyes with type 2 IMT showed significance in anatomical improvement but the visual function transiently improved at 3 months of treatment and showed no statistical significance at last visit, which caused by retinal atrophy from the natural course of the disorder.

The patients in this series response well to intravitreal ranibizumab therapy in both type 1 and 2 IMT. Like the previous study, the single case report by Ciarnella et al. with combined use of ranibizumab and laser photocoagulation was effective treatment for type 1 IMT patient. In contrast, Takayama et al. reported that intravitreal bevacizumab for 5 cases of type 1 IMT, did not show improvement of visual acuity or retinal edema, in this report did not mention about the duration of symptom before treatment. Previous reports in treatment of type 2 IMT, bevacizumab and ranibizumab reduced vascular leakage and macular edema with variable in improvement of visual acuity.

As we know, Anti-VEGF have the anti-edema and anti-angiogenic properties that could reduce vascular leakage, macular edema and exudation leading to an improvement in visual function. However recurrence may develop after discontinue the treatment.
From our results, the good response to the intravitreal injection of ranibizumab tend to be from; 1) variation in clinical course of the participant, in our series found that the patients with shorter duration of symptom (less than 3 months) had better result than longer duration (more than 3 months), 2) use of the different Anti-VEGF and method may show the different result.

However, one eye (case No. 6) in our series had visual loss after treatment with slightly decreased in CRT on OCT and no changed in leakage from FA. Visual loss was caused by intraretinal edema and exudates, but not related to the procedure or adverse event from ranibizumab.

We concluded that intravitreal ranibizumab injection might be the promising treatment for non proliferative stage of IMT type 1 and 2, in term of improvement of BCVA, decrease central retinal thickness and FA leakage. The limitations of the study are the small number of patients, retrospective study design and no control group. However, further studies with larger sample size and prospective comparative study design are required to determine the safety and efficacy of the treatment.

References


การรักษาภาวะเส้นเลือดผิดปกติที่จอรับภาพชนิดไม่สร้างเส้นเลือดใหม่ด้วยการฉีดยาบีซูแมบเข้าน้ําวุ้นตา

วิชัย ประสาทฤทธา, โสมศิริ สุขะวัชรินทร์, บุญทิพย์ ทิพย์สุริยาพร

บทคัดย่อ

บทนำ: ภาวะเส้นเลือดผิดปกติที่จอรับภาพเกิดจากการโป่งพองของเส้นเลือดขนาดเล็กรอบๆจุดรับภาพทำให้ระดับการมองเห็นลดลงในปัจจุบันมีการเสนอแนวทางการรักษาหลายวิธีเช่นการยิงเลเซอร์การฉีดยาเข้าน้ําวุ้นตา ซึ่งการตอบสนองต่อการรักษาไม่คงที่

วัตถุประสงค์: เพื่อประเมินผลการรักษาด้วยการฉีดยาบีซูแมบเข้าน้ําวุ้นตาในคนไทยที่มีภาวะเส้นเลือดผิดปกติที่จอรับภาพชนิดไม่สร้างเส้นเลือดใหม่

วิธีการศึกษา: ทำการเก็บข้อมูลย้อนหลังในผู้เข้าร่วมวิจัยจำนวน 10 คน (10 ตา) ที่มีภาวะเส้นเลือดผิดปกติที่จอรับภาพชนิดไม่สร้างเส้นเลือดใหม่และได้รับการรักษาด้วยการฉีดยาบีซูแมบขนาด 0.5 มิลลิกรัมเข้าน้ําวุ้นตาที่โรงพยาบาลรามาธิบดีในระยะเวลาตั้งแต่เดือนกรกฎาคม พ.ศ. 2555 ถึงเดือนมีนาคม พ.ศ. 2557 ซึ่งได้รับการเก็บข้อมูลและแปลผลการตรวจโดยจักษุแพทย์ด้านจอประสาทตา ประกอบไปด้วยระดับการมองเห็นที่ดีที่สุด,ภาพถ่ายจอประสาทตา,ภาพตัดขวางจอประสาทตาและการฉีดสีตรวจจอประสาทตา

ผลการศึกษา: อายุเฉลี่ยของผู้เข้าร่วมวิจัย 52.9 ± 9.7 ปี ค่ามัธยฐานของระยะเวลาการติดตามการรักษาคือ 12.0 (8.0 - 17.0) เดือน ค่ามัธยฐานของระดับการมองเห็นที่ดีที่สุดพบว่ามีค่าไม่ต่ำกว่า 0.35 (0.2 - 0.4) LogMAR เป็น 0.10 (0.0 - 0.3) LogMAR ที่ 3 เดือน และ 0.10 (0.0 - 0.4) LogMAR ที่การตรวจครั้งสุดท้าย ค่ามัธยฐานของความหนาที่จอรับภาพพบว่าลดลงจาก 374.3 ± 105.3 มิครอน ที่ก่อนเริ่มรักษาเป็น 257.4 ± 84.3 ในเดือนที่ 3 เดือนและ 242.4 ± 88.3 ในเดือนที่การตรวจครั้งสุดท้าย โดยพบว่าระดับการมองเห็นและความหนาของจอรับภาพมีการเปลี่ยนแปลงอย่างมีนัยสำคัญทางสถิติที่ 3 เดือนและการตรวจครั้งสุดท้ายเมื่อเปรียบเทียบกับก่อนเริ่มการรักษา ผลการเดินทางการรั่วซึมของเส้นเลือดคงที่คงอยู่ได้รับการรักษาและไม่พบภาวะแทรกซ้อนใด ๆ หลังรักษาเสร็จสิ้น

สรุป: การฉีดยาบีซูแมบเข้าน้ําวุ้นตาช่วยรักษาภาวะเส้นเลือดผิดปกติที่จอรับภาพชนิดไม่สร้างเส้นเลือดใหม่ได้โดยสามารถเพิ่มระดับการมองเห็น, ลดการเริ่มต้นของจอรับภาพ, และลดการรั่วซึมของเส้นเลือดจากการตรวจด้วยการฉีดยาบีซูแมบ

คําสั่งหุ่น: ภาวะเส้นเลือดผิดปกติที่จอรับภาพเส้นเลือดที่จอรับภาพมีการรักษาด้วยการฉีดยาบีซูแมบ

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