The Review of Clinical Use of Current Anti-VEGF Injections in Retinopathy of Prematurity

Prematüre Retinopatisinde Güncel Anti-VEGF Enjeksiyonu Klinik Uygulamalarının Gözden Geçirilmesi

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ABTRACT

Retinopathy of prematurity (ROP) is one of the major causes of visual loss in childhood in developed and developing countries. With the convenient screening and treatment methods, blindness due to ROP has significantly reduced. In Turkey, the incidence of ROP has been gradually increasing upon improved conditions of neonatal intensive care units. Conventional laser retinal photoablation therapy has provided effective results though it is inadequate in certain cases such as posterior ROP, small pupil and hazy ocular media. Additionally, laser photocoagulation destructs peripheral retina stopping the physiologic extension of normal blood vessels as well as abnormal ones. The intravitreal administration of anti-VEGF (vascular endothelial growth factor) injection is becoming more popular in the treatment of severe posterior ROP in the last few years. This article reviews the effectiveness of anti-VEGF applications in the treatment of ROP.

Key Words: Retinopathy of prematurity, anti-VEGF treatments, intravitreal injection.

ÖZ

Prematüre retinopatisi (PR), gelişmiş ve gelişmekte olan ülkelerdeki çocukluk çağı görme kayıplarının en önde gelen sebeplerindendir. Uygun tarama ve tedavi yöntemleri sayesinde PR'ne bağlı körlük artık belirgin şekilde azalmıştır. Ülkemizdeki yenidoğan yoğun bakım ünitelerinin koşullarında belirginleşmeye başlayan iyileşme, PR insidansında bir artışı da beraberinde getirmiştir. Retinanın geleneksel laserle ablasyonu oldukça etkili olsa da posterior PR, küçük pupil veya retinanın herhangi bir sebeple görülemediği bazı durumlarda uygulanamamaktadır. Ayrıca, periferik retinanın laserle fotoablasyonu anormal damarlanma yanında normal damar gelişimini da kesintiye uğratmaktadır. Son yıllarda, ciddi posterior PR'de intravitreal anti-VEGF (vasküler endotel büyüme faktörü) uygulaması artan şekilde popülarite kazanmıştır. Bu makale, PR tedavisinde güncel anti-VEGF uygulamalarının etkinliğini derlemiştir.

Anahtar Kelimeler: Prematüre retinopatisi, anti-VEGF tedaviler, intravitreal enjeksiyon.

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Geliş Tarihi - Received: 17.01.2015
Kabul Tarihi - Accepted: 05.06.2015
Ret-Vit 2015;23:189-194

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INTRODUCTION

Retinopathy of prematurity (ROP) is a disease of premature infants whose retinal vascularization is incomplete at 40 weeks gestation and it is associated with early gestational age and low-birth weight. When they are expose to high oxygen level, an abnormal growth and differentiation of retinal vasculature develop.[1,2] ROP is classified according to zones, stages and presences of plus disease. Zone I (posterior zone) is a circle that is twice the distance between the optic disc and the macula. Zone II encloses the zone I and extends to the nasal retina. Zone III covers zone II and the rest of all retinal areas especially temporal retina (Figure 1). There are different stages for the description of interface between vascular and avascular areas in ROP: Stage 1 indicates a line (between vascular and avascular retina), stage 2 indicates a ridge and stage 3 indicates neovascularization from interface toward the vitreous. Stages 4 and 5 include partial and total retinal detachment respectively (Figure 2).[3] Plus disease includes any one of vascular tortuosity, vitreus haze and rubeosis iridis at any stages that shows major complicating factor.

BASIS OF ANTI-VEGF THERAPY

The pathogenesis of ROP is complicated and multifactorial. Beside oxidative stress, growth factors play critical roles. Vascular endothelial growth factor (VEGF) is a potent growth factor in both phases of ROP and it is important for both physiological retinal vasculature and photoreceptors.[4] ROP involves two consecutive phases: The first phase is derived from hyperoxia and it is characterized by decreased VEGF levels, while the second phase is derived from exposure to relative hypoxia and increased VEGF levels at immature retinal tissue.[5] Diffuse avascular retinal areas take place in the first phase lasting till aproximately 32 weeks of gestational age. In the subsequent second phase, a VEGF burst occurs from the interface of the avascular and vascular areas of the retina leading to neovascularization and retinal distortion.[6]

Anti-VEGF administration has been shown to be effective in decreasing the neovascularization in oxygen-induced-retinopathy animal models.[7] Successful results of intravitreal injections of anti-VEGF agents in premature infants have increasingly been reported.[5,8,9] Anti-VEGF agents are used as mono[5,8-17] (Table I) or combined therapy[18-30] (Table II) or adjunctive to the surgery[14,21,31] in ROP (Table III).

So far there are 3 anti-VEGF agents that were applied for the therapy of ROP:

1. Bevacizumab (Altuzan®)

Bevacizumab is a monoclonal antibody of VEGF that has been approved for the treatment of colorectal cancer.[32] It is also currently been used in exudative age-related macular degeneration in adults.[33] The clinical use of bevacizumab in the treatment of severe ROP caused dramatic regression of neovascularization allowing the completion of the vascularization of avascular retinal area.[5]

The biggest multicenter randomized trial 'Bevacizumab eliminates the angiogenic threat of retinopathy of prematurity' (BEAT-ROP) in 150 infants with stage 3 + ROP which was reported in 2011. A significant benefit was demostrated in zone I disease with intravitreal bevacizumab (0.625 mg) when compared to laser therapy. The recurrence rate of bevacizumab monotherapy is lower than that of the conventional laser therapy (late recurrences appeared with bevacizumab at 54 weeks).[12] This study reported that seven infants died following the administration of intravitreal bevacizumab injection which might be attributed to the anti-VEGF agent itself.[12]

2. Pegaptanip Sodium (Macugen®)

Bevacizumab inhibits all VEGF isoforms in which some of them are related to the normal physiologic vascularization. Pegaptanip sodium is a selective VEGF-165 inhibitor which might be safe for both ocular and systemic use as VEGF-165 is responsible for most of the abnormal vasculogenesis.[4]

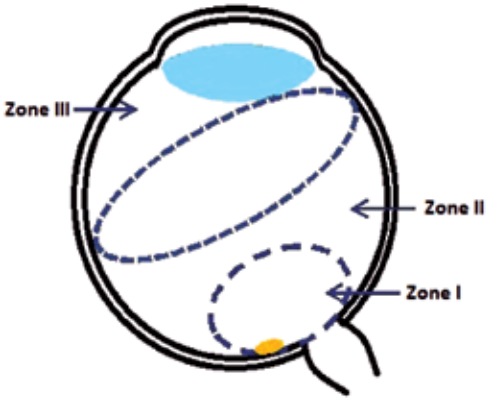

Figure 1: *The scheme of the right eye demonstrating zones of retinopathy of prematurity.*

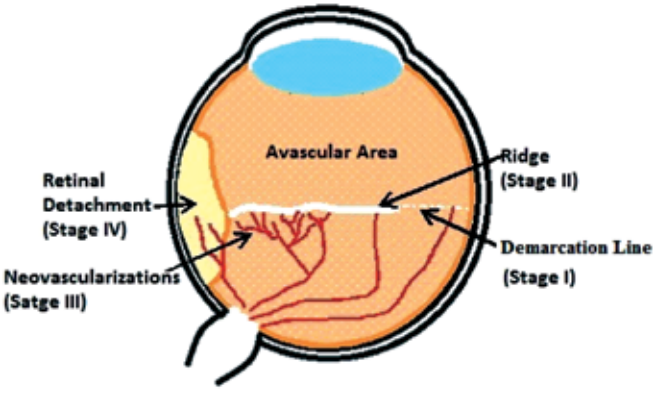

Figure 2: *The scheme of the left eye demonstrating stages of retinopathy of prematurity.*

Table 1: *The studies have reported the use of intravitreal anti-VEGF as monotherapy for ROP.*

Study (year)	Therapy	Patients (eyes)	Study design	Regression rate	Stage	Details
Quiroz Mercado et al.[5] (2008)	Bevacizumab (1.25 mg)	13 (18)	Prospective	88%	Stage 3 or 4	TRD developed in 2 eyes
Honda et al.[8] (2008)	Bevacizumab (0.4 mg)	1 (1)	Case report	0%	Stage 4	TRD developed
Mintz-Hittner et al.[9] (2008)	Bevacizumab (0.625 mg)	11 (22)	Retrospective	100%	Stage 3 Zone I	
Salman et al.[10] (2010)	Bevacizumab	9 (18)	Prospective	100%	Stage 3 Zone I or II	Re-injections needed in 6 eyes
Dorta and Kychental.[11] (2010)	Bevacizumab (0.625 mg)	7 (12)	Case series	100%	Type 1 ROP	
Mintz-Hittner et al.[12] (2011)	Bevacizumab (0.625 mg)	70 (140)	Prospective-randomised	95%	Stage 3 Zone I or II	Recurrence in 8 eyes macular fold developed in 1 eye following salvage laser
Harder et al.[13] (2011)	Bevacizumab (0.325 mg)	12 (23)	Retrospective	95%	Threshold ROP	
Wu et al.[14]	Bevacizumab (2011)	24 (43)	Retrospective	90%	Stage 3 or 4	Recurrence in 4 eyes
Wu et al.[15] (2013)	Bevacizumab (0.625 mg)	85 (162)	Retrospective	88%	Prethreshold ROP	Recurrence in 14 eyes
Castellano et al.[16] (2013)	Ranibizumab (0.25 mg)	3 (6)	Case series	100%	Prethreshold or Threshold ROP	
Sahin et al.[17] (2013)	Bevacizumab (0.625 mg)	13 (13)	Retrospective	85%	Type 1 ROP	Recurrence in 1 eye; TRD developed in 1 eye

TRD; Tractional Retinal Detachment.

Pegaptanip when combined with laser, showed rapid regression of neovascularisation without any ocular and side effect.[30] Late recurrence was observed with pegaptanip similar to bevacizumab since then the clinicians have decided to use anti-VEGF agents combined to the laser.[13-15]

3. Ranibizumab (Lucentis®)

Ranibizumab is another anti-VEGF agent that acts in similar way to bevacizumab but passes systemic circulation less than bevacizumab.[34] There are some reports regarding intravitreal ranibizumab use in ROP as a safe and effective treatment.[16,24,28,29] The systemic half-life time of ranibizumab is shorter than that of bevacizumab which would be an advantage in reducing systemic complications though it may necessitate frequent re-injections.[35]

THE APPLICATION OF INTRAVITREAL INJECTION

Anti-VEGF agents can be administered by an experienced retinal physician in the service setting under local anesthesia with sedation or rarely with general anesthesia. Under sterile conditions, the drug is administered at 0.5-2 mm posterior to the limbus using a 30-gauge needle connected to an insulin syringe.[5,18]

LASER AND VITREORETINAL SURGERY

Anti-VEGF agents are more effective than conventional laser in posterior ROP.[36] Additionally anti-VEGF agents can be administered under local anesthesia without the need of complicated equipment. Since they are not ablative, anti-VEGF drugs allow the completion of physiologic retinal vascularization. Refractive erros are more commonly encountered with laser treatment when compared to anti-VEGF monotherapy.[37] No macular fold secondary to anti-VEGF was reported in infants.[36,37] However, laser retinal photoablation is still a gold standard for the treatment of ROP currently untill the hugely populated case-controlled long-term follow-up studies regarding anti-VEGF treament is available.

Laser and anti-VEGF treatment have similar mechanism in decreasing excessive VEGF levels.[4] To date, laser treatment seemed well effective in conjunction with anti-VEGF[18,28,30] for the treatment of ROP, but the safety of this combination has not been fully established.[5] Anti-VEGF agents probably pass into the systemic circulation much easier when combined to laser as the laser damages intact retinal tissue.

Table 2: *The list of literature using anti-VEGF agents with salvage or adjunct to conventional laser therapy.*

Study (year)	Combined to laser	Patients (eyes)	Study design	Outcome of Regression rate	Stage	Details
Chung et al.[18] (2007)	Bevacizumab (0.75 mg)	1 (2)	Case report	100%	Stage 3 Zone I	
Lalwani et al.[19] (2008)	Bevacizumab (1.25-0.625 mg)	3 (5)	Case series	80%	Threshold ROP	
Nazari et al.[20] (2010)	Bevacizumab (0.625 mg)	8 (14)	Prospective	100%	Severe ROP	
Law et al.[21] (2010)	Bevacizumab (0.75 mg)	5 (11)	Retrospective	82%	AP-ROP	TRD developed in 2 eyes
Lee et al.[22] (2010)	Bevacizumab (0.5 mg)	8 (16)	Retrospective	100%	Stage 3 Zone I or II	
Erol et al.[23] (2010)	Bevacizumab (0.625 mg)	4 (7)	Case series	86%	Stage 3 Zone I or II	
Jang et al.[24] (2010)	Ranibizumab (0.30 mg)	1 (2)	Case report	0%	Stage 3 Zone I	Progressed to RD
Wutthiworawong et al.[25] (2011)	Bevacizumab	12 (23)	Retrospective	100%	APROP	
Axer-Siegel et al.[26] (2011)	Bevacizumab (0.75 mg)	4 (8)	Case series	100%	Stage 3 Zone I or II	macular fold developed in 1 eye
Ozdek et al.[27] (2012)	Bevacizumab (0.625 mg)	9 (15)	Retrospective	40%	AP-ROP	
Mota et al.[28] (2012)	Ranibizumab (0.30 mg)	2 (4)	Case series	100%	AP-ROP	
Lin et al.[29] (2012)	Ranibizumab (0.25 mg)	1 (2)	Case report	100%	Stage 3 Zone I	Unresponsive to previous bevacizumab monotherapy
Autrata et al.[30] (2012)	Pegabtanib (0.30 mg)	34 (68)	Prospective	90%	Stage 3 Zone I or II	

AP-ROP; Aggresive Posterior Retinopathy Of Prematurity, TRD; Tractional Retinal Detachment, RD; Retinal Detachment.

Table 3: *The outcome of studies reported use of intravitreal anti-VEGF prior the vitrectomy.*

Study (year)	Adjunctive to vitrectomy	Patients (eyes)	Study design	Outcome of Regression rate	Stage
Law et al.[21] (2010)	Bevacizumab (0.75 mg)	2 (2)	Case series	50%	APROP
Wu et al.[14] (2011)	Bevacizumab (0.625 mg)	3 (6)	Case series	100%	Stage 4 or 5
Xu et al.[31] (2013)	Bevacizumab (0.625 mg)	8 (12)	Retrospective	100%	Stage 4

AP-ROP; Aggresive Posterior Retinopathy Of Prematurity.

Vitreoretinal surgery is required for the last stages of ROP with retinal detachment. The success of the surgery is impressed from the regression of plus diseases and neovascular activity.[31] Anti-VEGF prior to vitrectomy in prematures has been reported to be effective in the reduction of neovascular activity and it offers good anatomical outcomes than without anti-VEGF group.[31] Anti-VEGF provides early surgical intervention, less intraoperative bleeding with shortened surgery time. The worsening of retinal detachment was noticed after the administration of bevacizumab injection in some cases with tractional membranes. The authors recommend early surgery following injections in such cases.[8,31]

DOSING REGIMEN

Appropriate dosage of anti-VEGF is not yet determined. The range changes from 0.375 to 1.25 mg in different studies.[5,12,13] A recent study in mouse model with bevacizumab showed effective inhibiton of retinal neovascularization from low (0.625 µg) to high (2.5 µg) drug doses, though a limited toxicity was

demonstrated with high doses.[38] Another study determined a dose dependent apoptosis of photoreceptors and other cells that were induced by intravitreal bevacizumab in rabbit retinal tissue.[39] The timing of injection is not certain and generally recommended after 31 or 34 weeks in different studies as early injections may disturb the retinal differentiation and vascularization.[22,40] Further studies are needed to clarify the lowest dose for effective treatment as well as the best timing for anti-VEGF treatment for ROP.

ADVERSE EFFECTS

Intravitreal use of bevacizumab has been shown to get out from the eye through choriocapillaris in nonhuman primates.[41] Decreased serum VEGF levels and potent effect in fellow eyes were also reported following the use of intravitreal anti-VEGF.[42] Infants are expected to have increased risk for systemic effects of intravitreal drug when compared to adults because of their impaired blood-retinal barrier and smaller body mass index, though such effects have not been reported yet.[13]

Combined therapy with laser offers favourable results without any reported late recurrence. However, a possible acces of intravitreal drug into the systemic circulation from ablated retina should be kept in mind.[18] On the other hand, combination with laser could decrease the need for repeated injections of anti-VEGF that eliminates cumulative drug dose.[43] Lastly, anti-VEGF agents are newly recognised molecules. There is no adequate data about their pharmacodynamic and pharmacokinetic effects in infants.[44]

It should also be noted that bevacizumab inhibits all VEGF isoforms. However, VEGF is necessary for organogenesis. BEAT-ROP trial reported some infant deaths from lung failure.[13]

Anti-VEGF accelerates acute contraction of tractional retinal detachment.[8,31] It should be carefully used in the vitrectomy. On the other hand, as conventional laser therapy is ineffective at posterior ROP that appeared in approximately one tenth of retinopathy infants, anti-VEGF should be first choice in such cases.[43]

Intravitreal injections have been reported to cause cataract, endopthalmitis and retinal detachment in adult population although not yet reported in infants.[43] Ischemic optic neuropathy, retinal artery and venous occlusions are reported to be rare ocular adverse effects from the use of anti-VEGF agents in adults.[45,46]

SUMMARY

Intravitreal injection of anti-VEGF agents is the current effective treatment modality in ROP although they are still in off-label use. In the near future, ROP treatment will not be accomplished without the use of anti-VEGF. Side effects, frequency and dosing regimens as well as safety, effectivity and late recurrency issues should be studied by further meta-analyses. What we are almost sure for now is to administer anti-VEGF for some cases of ROP in which laser can not be delivered because of hazy ocular media or posterior localization of the disease.[47,48]

In conclusion, the clinicians should consider the potential risks and benefits of anti-VEGF treatment for ROP and should be followed-up their treated infants for late recurrences. Because, local and systemic safety of anti-VEGF agents for infants understandable with large animal and phase 1 human studies in course of time.

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