

X'e Bağlı Juvenil Retinoskizisde Topikal Brinzolamid Tedavisi Sonuçlarımız

Results of Topical Brinzolamide Treatment in Patients Diagnosed As X-linked Retinischisis

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ÖZ

Amaç: X'e bağlı juvenil retinoskizis tanımlı hastalarda topikal brinzolamid tedavisi sonuçlarını değerlendirmek.

Materyal - Metod: Ocak 2010- Ocak 2016 tarihleri arasında X'e bağlı juvenil retinoskizis tanısı konulan 16 hastanın dosyaları geriye dönük olarak incelendi. Topikal brinzolamid tedavisi başlanan, 12 ay ve üzeri takibi olan 8 hastanın 16 gözü çalışmaya dahil edilerek en iyi düzeltilmiş görme keskinliği (EİDGK) ve santral maküler kalınlıklarındaki (SMK) değişiklikler değerlendirildi.

Bulgular: Ortalama yaş 12,8±4,2 yıl (6-18 yıl) ve ortalama takip süresi 36,0±24,0 ay (12-84 ay) olarak bulundu. İlk muayenedeki ortanca EİDGK Snellen eşeli ile 0,2 (Aralık: 0,1-0,6) iken ortalama SMK 509,3±124,7 mikron (Aralık: 215-646 mikron) olarak ölçüldü. Hastalara brinzolamid damla günde 3x1 olarak reçete edildi. Son muayenedeki ortanca EİDGK 0,25 (Aralık: 0,1-0,7) iken ortalama SMK 457,8±135,6 mikron (Aralık: 202-714 mikron) olarak ölçüldü. İlk ve son muayenedeki EİDGK ve SMK arasında istatistiksel olarak anlamlı fark mevcuttu (p<0,05). Dokuz gözde Snellen eşelinde en az 1 sıra ve üzeri artış olurken, 6 gözde görme keskinliği aynı seviyede idi. Sadece bir gözde SMK azalmasına rağmen görme keskinliğinde azalma olduğu saptandı. Takiplerde 4 gözde %20 ve üzeri, 4 gözde %10-20 arası, 5 gözde %10 altı SMK'da düşme saptandı. Üç gözde ise tedaviye rağmen SMK'da kalınlaşma olduğu görüldü.

Sonuç: X'e bağlı maküler retinoskizisli hastalarda topikal brinzolamid ile hem görme keskinliğinde kazanım, hem de optik koherens tomografide görece stabilizasyon sağlanabilmektedir.

Anahtar kelimeler: Görme keskinliği, maküla kalınlığı, maküler skizis, karbonik anhidraz inhibitörü, optik koherens tomografi.

ABSTRACT

Purpose: To evaluate the result of topical brinzolamide treatment in patients diagnosed as X-linked juvenile retinoschisis (XLRS).

Subjects and Methods: We retrospectively screened files of 16 patients with XLRS diagnosed between January, 2010 and January, 2016 and 16 eyes of 8 patients who were on topical brinzolamide treatment for at least 12 months or more were included to the study. Changes in best-corrected visual acuity (BCVA) and central macular thickness (CMT) were evaluated.

Results: Mean age 12.8±4.2 years (range: 6-18 years) and the mean follow-up time was 36.0±24.0 months (range: 12-84 months) in our patients. Median BCVA with Snellen chart was 0.2 (range: 0.1-0.6) and mean CMT was 509.3±124.7 micron (range: 215-646 micron) at the baseline. Topical brinzolamide was prescribed as tid in all patients. Median BCVA was 0.25 (range: 0.1-0.7) and mean CMT was 457.8±135.6 micron (range: 202-714 micron) at the last visit. There was a statistical difference in baseline and final BCVA and CMT (p<0.05). The BCVA improved more than one-order in 9 eyes, unchanged in six eyes and was worsened more than one-order in one eye despite the decrease of CMT. A reduction of at least 20% in CMT was achieved in 4 eyes whereas 10-20% in 4 eyes and below 10% in 5 eyes at the end of follow-up. CMT increase was observed in 3 eyes despite the topical brinzolamide treatment.

Conclusion: In patients with XLRS, topical brinzolamide administration may provide some improvement in visual acuity and relative stabilization in central macular thickness.

Key Words: Carbonic anhydrase inhibitors, macular schisis, macular thickness, optic coherence tomography, visual acuity.

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INTRODUCTION

Clinical entities associated with macular schisis include X-linked juvenile retinoschisis and NR2E3 mutation-related disorders (enhanced S-cone syndrome).^{1, 2} The X-linked juvenile retinoschisis (XLRS) was first defined as separation of retinal layers in 1898 and X-linked inheritance was discovered in 1913.^{1, 3-6} Retinoschisin protein is a constitutional protein that is secreted by photoreceptors and bipolar cells, binding specifically and strongly to surface of several cell in retina and enabling intracellular adhesion. The disease is caused by a mutation in RS1 gene encoding retinoschisin protein.^{3, 7} Its prevalence ranges from 1/5000 to 1/25,000 and visual acuity is generally between 1/10 and 4/10. Macular atrophy usually develops at decades 4 and 5. Macular schisis is observed in all patients while peripheral schisis by 50%, rhegmatogenous retinal detachment by 5-10% and vitreous hemorrhage by 4-10%. No leakage is observed in macular schisis on fundus fluorescein angiography while hyper-autofluorescence bicycle-wheel pattern is observed on fundus autofluorescence imaging.^{1, 3, 4, 8, 9} On optic coherence tomography, neurosensory retinal detachment and bridging of retinal elements are observed.^{6, 10} When details of neurosensory retinal detachment are characterized, schisis in internal nuclear layer is seen by 6.3% whereas schisis in ganglion cell layer and internal nuclear by 75%, schisis in internal nuclear layer and outer plexiform layer by 12.5% and schisis in ganglion cell layer, internal nuclear layer and outer plexiform layer by 6.3%.¹¹ In addition, it has been suggested that there are changes perifoveal superficial and profound vascular plexus; in particular, alterations in profound vascular plexus may be associated to prognosis.¹²

Topical and/or oral carbonic anhydrase inhibitors are used mainly in the treatment of macular schisis; in additions pars plana vitrectomy is undertaken when indicated. In addition, gene therapy trials are ongoing.¹³⁻²² In our study, effectiveness of topical brinzolamide treatment was investigated in 16 eyes of 8 cases with X-linked retinoschisis.

MATERIAL - METHOD

We retrospectively screened files of 16 patients diagnosed as X-linked juvenile retinoschisis between January, 2010 and January, 2016. Sixteen eyes of 8 patients who received topical carbonic anhydrase inhibitor for at least ≥ 12 months and had optic coherence tomography images were included to the study. In all patients, the best corrected visual acuity (BCVA) measurements and anterior segment examination by slit lamp were performed at baseline and final visit. The intraocular pressure was measured by Goldmann applanation tonometry and detailed funduscopy was performed under dilatation. Macular thickness was assessed by optic coherence tomography (HRA Spectralis) (Heidelberg

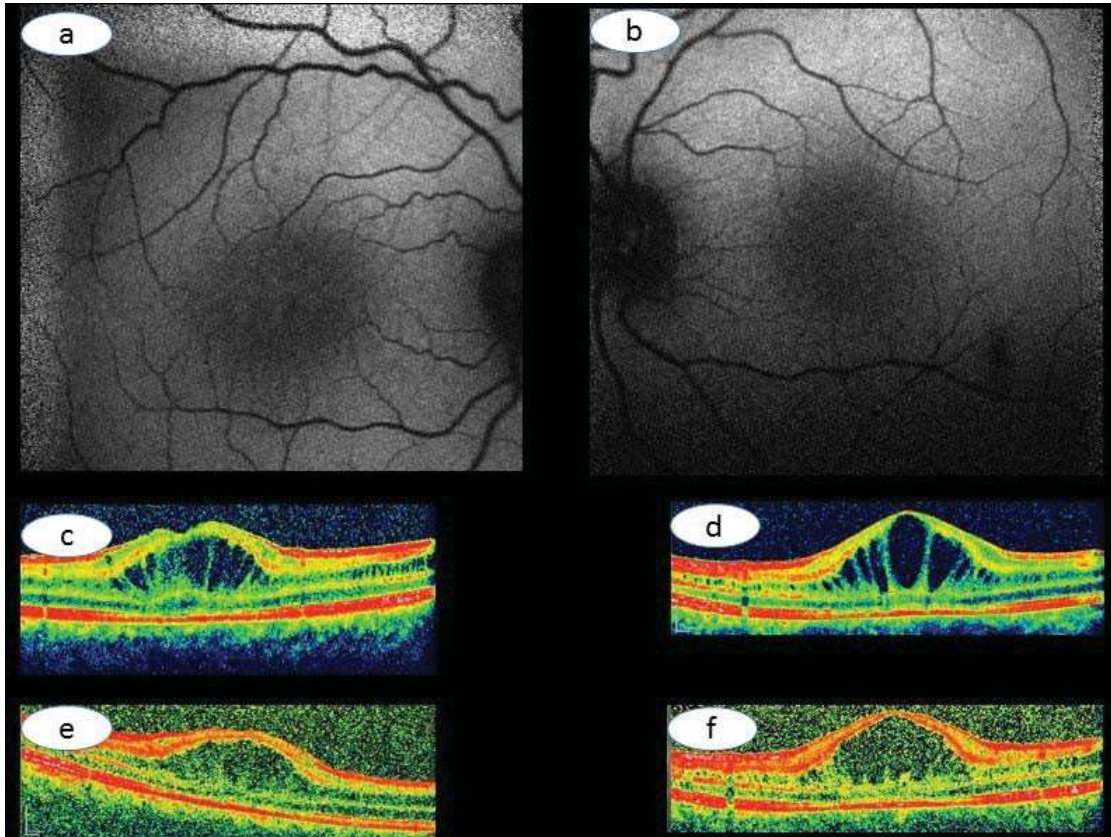
Engineering, Heilderberg, Germany). In all patients, 1% brinzolamide (Azopt[®], Alcon, Puurs, Belgium) was prescribed three times daily. Positive treatment response was defined as reduction $\geq 20\%$ in macular thickness during follow-up. The visual acuity and macular thickness changes at baseline and final control visit were compared in our study.

FINDINGS

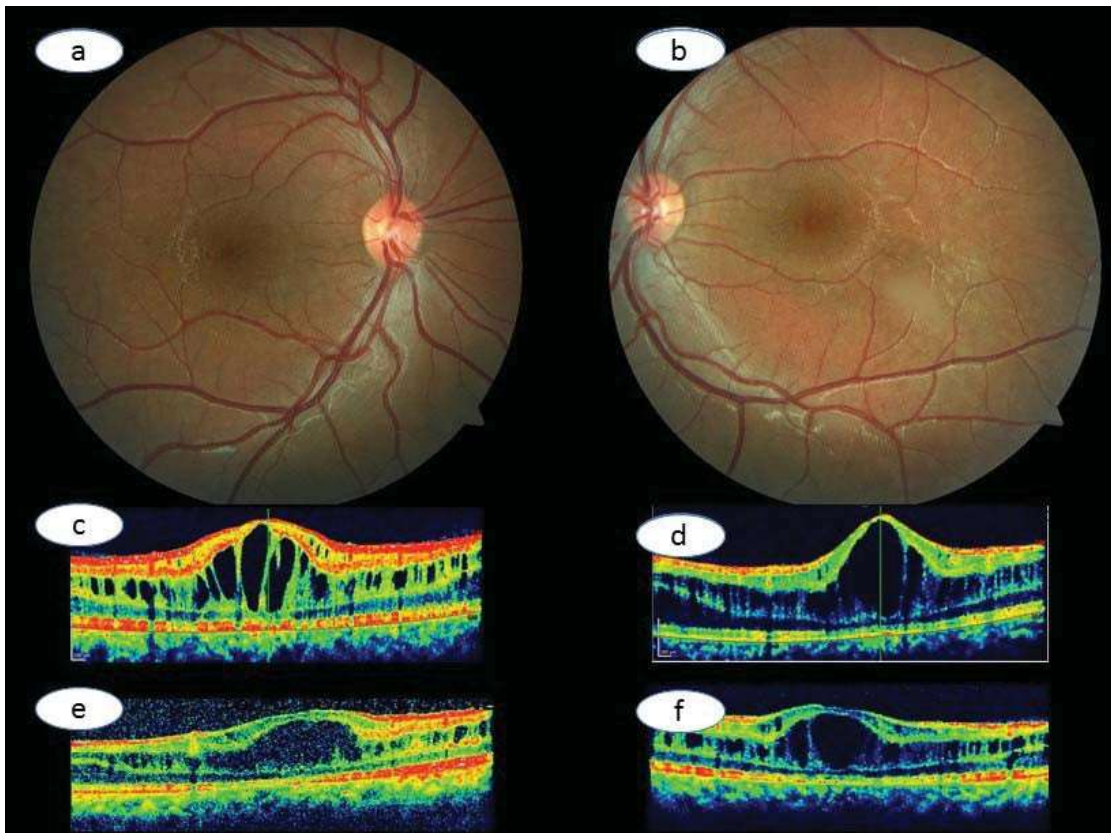
All patients were male. Mean age was 12.8 ± 4.2 years (range: 6-18) and mean follow-up was 36.0 ± 24.0 months (range: 12-84). Retinoschisis was present in both maculae in all patients. In 3 patients, peripheral retinal schisis was present in addition to macular schisis. At baseline, median BCVA as rated by Snellen charts was 0.2 (range: 0.1-0.6) while mean CMT was 509.3 ± 124.7 micron (range: 215-646). In all patients, 1% brinzolamide was prescribed three times daily. In final control visit median BCVA was measured as 0.25 (range: 0.1-0.7) while CMT was measured as 457.8 ± 135.6 micron (range: 202-714). There was significant difference in BCVA and CMT values obtained at baseline and final control visit ($p < 0.05$). It was seen that there was \geq one order improvement in Snellen charts in 9 eyes while visual acuity was at similar levels in 6 eyes. It was found that visual acuity was decreased despite decreased CMT in only one eye. In follow-up, there was 20% reduction in CMT in 4 eyes, 10-20% reduction in 4 eyes and $< 10\%$ in 5 eyes. It was seen that there was increase in CMT despite treatment in 3 eyes. Pictures 1 and 2 present treatment responses in 4 eyes from 2 case. No rhegmatogenous retinal detachment or vitreous hemorrhage development was observed during follow-up. Table 1 presents demographic and clinical characteristics in our patients.

DISCUSSION

Carbonic anhydrase inhibitors increase pumping subretinal fluid, enhancing adhesion of retinal layers and inducing retinoschisis.^{15, 19} The reduction by 20-25% in macular thickness is considered positive treatment response. In their study on 22 eyes of 11 patients, Gurbaxani et al ark.¹⁹ prospectively evaluated changes in visual acuity and on OCT after 3-months treatment with oral acetazolamide at a dose of 250 mg twice daily in patients weighing > 60 kg and 125 mg twice daily in patients weighing < 60 kg. Authors found that visual acuity was improved from 0.52 logMar to 0.46 logMar while mean macular thickness was reduced from 314 micron to 294 micron. In their study on 18 eyes of 9 patients, Verbakel et al.¹⁴ investigated effects of carbonic anhydrase inhibitors on visual acuity and foveal avascular zone thickness. The patients was prescribed oral acetazolamide at a dose 125 mg twice daily to 250 mg three times daily based on age and 6 patients were given additional topical carbonic anhydrase inhibitors (brinzolamide in 4 patients, and dorzolamide in 2 patients).



Picture 1: Fundus autofluorescence image at baseline examination (case 6); a) right eye b) left eye; OCT image c) right: 591 micron d) left: 630 micron. OCT image after 12-months topical brinzolamide therapy e) right: 520 micron, sol) 500 micron



Picture 2: Fundus autofluorescence image at baseline examination (case 7); a) right eye b) left eye; OCT image c) right: 536 micron d) left: 630 micron. OCT image after 24-months topical brinzolamide therapy e) right: 322 micron, left) 560 micron

Table 1: Demographic and clinical characteristics

#,Age, Gender	BCVA*				CMT** (micron)				CMT change (%)		Follow-up (months)
	ba sel ine		Fin al		ba sel ine		Fin al		Rig ht	left	
	Right	Left	Right	Left	Right	Left	Right	Left			
1/9/M	0.1	0.1	0.7	0.1	215	606	202	714	-6%	+17.8%	12
2/15/M	0.2	0.2	0.2	0.2	327	407	272	325	-16%	-20%	60
3/12/M	0.3	0.3	0.5	0.4	447	587	450	570	+0.6%	-2%	36
4/18/M	0.2	0.2	0.2	0.2	534	580	547	546	+2.4%	-5%	36
5/18/M	0.2	0.6	0.2	0.7	416	415	408	345	-1%	-16%	84
6/10/M	0.2	0.1	0.3	0.5	591	630	520	500	-12%	-20%	12
7/15/M	0.3	0.1	0.6	0.2	536	630	322	560	-58%	-11%	24
8/6/M	0.1	0.6	0.2	0.4	582	646	578	467	-0.6%	-27%	24

BCVA: Best-corrected visual acuity as rated Snellen charts, CMT: central macular thickness

Authors defined positive treatment response as reduction by 22.4% in macular thickness. In the study, mean follow-up was 6.8 months and macular thickness improvement was observed in 55% of patients. The improvement was achieved within first months in 80% of patients with improvement in macular thickness. In addition, visual acuity gain by 0.14 logMar was achieved in at least one eye in 33% of patients. Andreuzzi et al.²² retrospectively reviewed patients treated with carbonic anhydrase inhibitor between 2005 and 2015. The study included 68 eyes of 36 patients aged 5-61 years (mean age: 27.2 years). Topical dorzolamide was used in 31 patients whereas topical brinzolamide in 3 patients, oral acetazolamide in one patient and combined therapy in one patient. It was found that cyst was resolved in 45 eyes (66%) while no anatomical change was observed in 20 eyes (29%) on OCT. In addition, worsening was observed in 3 eyes (4%). Visual acuity gain was smaller than mean 1-order ETDRS. In one-third of eyes, it was found that macular thickness was re-increased when treatment was withdrawn. Yang et al.²³ treated 4 patients with XLRS by using topical brinzolamide. Authors reported decrease in cysts by 21-33% in only one eye of 2 patients and both eyes of one patient on OCT. In one patient, during control visits, macular thickness varied from decrease by 11% to increase by 19%. In that study, no significant difference was detected in visual acuity between pretreatment and post-treatment values.

In the literature, successful outcomes have been reported with vitrectomy in cases with progressive peripheral schisis.^{13, 17, 18} In their study on 28 eyes of 22 patients with progressive XLRS, Yu et al.¹³ performed vitrectomy in 17 eyes while they followed 11 eyes without treatment. Visual acuity was improved from 20/125 to 20/55 in surgery group while it was decreased from 20/100 to 20/400 in untreated group.

The schisis was resolved in all eyes underwent surgery. In control group, progression was observed in all eyes and retinal detachment (n=8) and vitreous hemorrhage (n=4) were developed. Authors suggested that vitrectomy may prevent complications threatening vision in progressive cases. Ikeda et al.¹⁸ performed pars plana vitrectomy in 5 eyes of 3 patients with XLRS. After surgery, schisis cavity was relieved in 4 of 5 eyes after surgery. Visual acuity was improved in 3 eyes while remained unchanged in 2 eyes. In our study, no patient required surgery for retinal detachment or vitreous in our study.

In conclusion, topical carbonic anhydrase inhibitor use ensures partial anatomical recovery and mild improvement in visual acuity in patients with X-linked retinoschisis.

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