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Intravitreal anti-VEGF treatment for retinopathy of prematurity in infants with active adenoviral keratoconjunctivitis

Running head: Adenoviral keratoconjunctivitis and ROP

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Abstract

Purpose: To evaluate the results of intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatment for retinopathy of prematurity (ROP) in infants with active adenoviral keratoconjunctivitis (AKC).

Material and Methods: A retrospective analysis was performed using the medical records of all infants treated with intravitreal injections of anti-VEGF agents during an AKC outbreak previously reported in the literature at a tertiary center for treatment of ROP. The infants were divided into two groups. Group-1 included nine infants (18 eyes) with AKC, while Group-2 included 13 infants (26 eyes) without AKC.

Results: During the AKC outbreak, 22 infants were treated with anti-VEGF agents for treatment-requiring ROP. In all patients in both groups the ROP and plus disease displayed a significant regression within two days after the intravitreal injections. Moreover, no serious complications such as endophthalmitis, retinal detachment, cataract or intravitreal hemorrhage were observed after the treatment and there were no statistically significant differences between the groups in terms of postoperative complications.

Conclusion: Immediate and appropriate intervention is very important in cases of treatment-requiring ROP otherwise it can result in blindness. However, laser treatment for ROP is technically difficult in infants with active AKC. The results of this study showed that favorable outcomes without serious ocular complications could be obtained via intravitreal injections of anti-VEGF agents in infants with active AKC.

Keywords: Adenoviral keratoconjunctivitis; intravitreal injection; retinopathy of prematurity; anti-vascular endothelial growth factor agents.
Introduction

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness, particularly in developing countries (1). This disorder in premature infants is characterized by the development of retinal neovascularization (2). The related literature clearly defines the role of vascular endothelial growth factor (VEGF) in the pathogenesis of ROP (3-5). Although laser photocoagulation (LPC) is the standard treatment for ROP, various studies have reported positive outcomes in relation to anti-VEGF agents used in ROP treatment (2,6-8).

Adenoviral serotypes commonly cause adenoviral keratoconjunctivitis (AKC), which represents one of the most common external ocular viral infections (9). Adenoviruses have double-stranded DNA and are roughly 80 to 110 nm in size. If kept at room temperature, they continue to be infectious for weeks. Hence, they tend to have a high potential for causing nosocomial infections (10). Adenovirus outbreaks at neonatal intensive care units (NICUs) have been reported in numerous studies and the association of AKC with ROP detection has been noted in the literature (11,12). Thus, AKC is an important comorbid factor, particularly in infants with treatment-requiring ROP.

However, performing ROP screening and laser treatment is technically difficult in eyes with active AKC, due to eyelid edema, conjunctival chemosis, hemorrhage from conjunctival membranes, and corneal haze.

The purpose of this study was to evaluate the results of intravitreal anti-VEGF treatment for ROP in infants with active AKC during an epidemic keratoconjunctivitis outbreak in a ROP treatment center.
Material and Methods

This single-center retrospective study was conducted at a tertiary center for the screening and treatment of ROP in the Adana Numune Training and Research Hospital (Adana, Turkey). The study was approved by the Ethics Committee of the hospital, and complied with the tenets of the Declaration of Helsinki. Informed consent was obtained from the parents of all patients. As previously reported in the literature (13), an outbreak of AKC occurred in the center between January 2015 and September 2015. Medical data in the follow-up charts for this period were reviewed, and infants who had been treated with intravitreal anti-VEGF agents were included in this study. Infants with treatment-requiring ROP were defined according to the results of the Early Treatment for ROP study (14). Anti-VEGF treatment had been recommended in infants with treatment-requiring ROP in the posterior zone (Zone-1 or Posterior zone-2). The diagnosis of AKC was carried out via biomicroscopic examination and positive family findings. The effects and potential ocular and systemic adverse effects of anti-VEGF agents (bevacizumab, ranibizumab or aflibercept) and laser photocoagulation (LPC) were explained to the families, and treatment choice was made according to their preferences. The infants treated for ROP with anti-VEGF agents during this period were divided into two groups. Group-1 included infants with AKC, while Group-2 included infants without AKC.

As standard screening procedure, all examinations were performed in the unit for premature infants and disposable eyelid speculums and depressors were used for ROP examinations. Birth weight (BW), gestational age (GA), zones, presence of rubeosis iridis or plus disease, postconceptional age (PCA) at treatment, complications, and reactivation of disease were recorded. Retinal images were obtained using the Heine Video OMEGA® 2C binocular indirect ophthalmoscope (Heine Optotechnik, Herrsching, Germany). The number of patients routinely examined had decreased during the outbreak, and all preventive precautions were
taken. However, control of the outbreak at the center was made more difficult because, as a reference center for the treatment of ROP, it continued to provide services.

Intravitreal anti-VEGF injections were performed in the operating theater under topical anesthesia by the same surgeon (EAS) as previously described (7,8). Povidone iodine 5% was applied to the ocular surface prior to the injections. After the injections, ophthalmic examinations were performed to check the central retinal artery perfusion and the intraocular pressure. Topical antibiotic drops were administered as postoperative prophylaxis four times a day for a week. Biomicroscopic and indirect fundoscopic examinations were performed on the first and third days after the procedure, and later on a biweekly basis until vascularization of the peripheral retina was completed.

Postoperative ocular adverse effects, including signs of intraocular inflammation or endophthalmitis, intraocular pressure elevation, and secondary cataract formation, were recorded. The infants with AKC were more carefully examined, particularly in terms of postoperative vitreous haze or endophthalmitis. Systemic adverse effects were closely monitored during the perioperative and postoperative periods in the NICU. This included continuous monitoring of blood pressure, oxygen saturation, and heart rate. Respiratory and cardiac rates and urinary or allergic side effects (rash or bronchospasm) were also monitored.

Data analysis was performed using the Statistical Package for Social Sciences for Windows software (SPSS version 16.0, SPSS Inc., Chicago, USA). The descriptive statistics of normally distributed continuous variables were expressed as mean ± standard deviation. Variables were compared using the Mann–Whitney U test. Categorical variables were presented as frequency (%) and the groups were compared using the Chi-Square and Fisher’s exact tests. Differences were considered statistically significant at $p < 0.05$. 
Results

Four hundred and forty-five infants were screened retrospectively during this outbreak period. Fourteen percent (61/445) of the infants required ROP treatment with either LPC or intravitreal anti-VEGF therapy. Twenty-two infants were administered intravitreal anti-VEGF agents for treatment-requiring ROP, and included nine infants (18 eyes) in Group-1 and 13 infants (26 eyes) in Group-2.

There were no significant differences between the groups regarding demographic features, the baseline characteristics of ROP and post treatment clinical findings.

The demographic characteristics and clinical findings with p values for both groups are presented in Table 1.

In Figure 1, photographs can be seen of an infant from Group-1 with treatment-requiring ROP and active AKC.

The mean follow-up time was 20.4 ± 4.68 months (Range, 18-24 months) in Group-1 and 20.1 ± 3.97 months (Range, 18-24 months) in Group-2. None of the cases in either group was observed to have any complications caused by the injections in the early or late postoperative period. Prior to the intravitreal injections, there had been concern that the Group-1 ROP cases would develop postoperative endophthalmitis or vitreous haze due to the active AKC. However, none of these cases developed any endophthalmitis or vitreous haze. In terms of postoperative complications, there were no statistically significant differences between Group-1 and Group-2.

All eyes of both groups displayed a rapid regression of ROP after a single injection of anti-VEGF agents. In both groups, complete regression of plus disease was seen in the 1st week post treatment. The treated eyes displayed no severe ocular complications and no cataracts,
tractional or rhegmatogenous retinal detachment, intravitreal hemorrhage, or endophthalmitis occurred in either group.

Intraocular pressure measurements were normal at all the postoperative examinations.

**Discussion**

Adenoviruses lead to a highly contagious infectious disease primarily involving the ocular surface. The common form of adenoviruses is epidemic keratoconjunctivitis (EKC) which is responsible for NICU outbreaks. The viral incubation time ranges from 2 to 12 days (15,16). Transmission occurs mainly via direct contact, the fecal-oral route, medical instruments and aerosols. Resistance to the external environment is quite high (17) and therefore, infants in NICUs can suffer during outbreaks due to adenovirus infections.

Retinopathy of prematurity is a neovascular retinal disorder of premature infants in which the avascular part of the retina triggers VEGF production. Routine ROP screenings start at the postnatal fourth week, and then weekly or bi-weekly examinations are performed during the follow-up period. In the case of treatment-requiring ROP, timely and appropriate intervention is very important. Unless it is urgently treated, the accumulation of VEGF eventually leads to retinal detachment (2). However, the screening and treatment of ROP is difficult in infants with AKC due to ocular symptoms such as eyelid swelling, corneal edema, conjunctival injection and follicles, chemosis, and pseudomembrane formation(18). The related literature provides no information about the effects of intravitreal anti-VEGFs applied as ROP treatment in infants with AKC. One study reported laser photocoagulation (LPC) treatment for ROP in an infant with AKC where in it was recommended that the procedure be stopped and a second laser session arranged so that laser ablation of the remaining avascular zones could be completed (19). In our practice, the application of laser photocoagulation (LPC) was technically difficult at every step. Due to eyelid edema and chemosis, the eyelid speculum was incapable of sufficiently opening the eyes. The fundus could not be easily seen and the laser spots were unable to focus on the retinas because of the corneal haze and hemorrhage from conjunctival membranes, and the attempts to apply LPC were in fact unsuccessful. In cases of ROP, retinal detachment can result if timely appropriate treatment is not given. Therefore, during this outbreak, the unusual decision was taken to choose intravitreal injection
of anti-VEGF agents for treatment of ROP. The infants with active AKC who were diagnosed as treatment-requiring ROP were administered intravitreal anti-VEGF injections, and satisfying outcomes were obtained. Moreover, no endophthalmitis or serious ocular side effects were observed. A search of the related literature in terms of adenoviral endophthalmitis revealed no information about this issue.

The standard procedure of preoperative ocular surface cleaning has been previously defined as waiting for 3 min after applying povidone iodine 5%. Povidone iodine 2.5% was found by some authors to be an effective treatment in AKC (17). In the present study, the washing of the ocular surface with povidone iodine 5% and waiting 5 min before injection might have been effective in decreasing the conjunctival virus load.

Unlike ROP, AKC is an ocular surface disease which is believed to have no effect on retinal vascular disease. The present study aimed to identify whether there were differences in the efficiency of the anti-VEGF agents applied intravitreally via the transconjunctival route over the virus-loaded conjunctiva. Postoperative findings of Group-1 and Group-2 were compared statistically, and similar clinical outcomes were obtained in both groups. Therefore, AKC was considered to have had no effects on the efficiency of the anti-VEGFs applied in the ROP treatment.

Some limitations of the present study included its retrospective nature, the small sample size and the short follow-up time. One of the most important limitations of the study is lack of virus serotyping with polymerase chain reaction (PCR). Because PCR is a very costly technique not funded by the health system, and was thus not available in the study hospital. However, PCR could be performed for only 2 patients during this outbreak and adenovirus type 8 isolated. As the patients were not in the study groups, we did not mention it in this study. But, the patients in the study had similar clinical features like patients tested.
In conclusion, in case of treatment-requiring ROP, timely and appropriate intervention is very important. However, LPC treatment for ROP is technically difficult in infants with active AKC. The results of this study showed that favorable outcomes without serious ocular complications could be obtained via intravitreal injections of anti-VEGF agents in infants with active AKC.

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Declaration of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

References


**Figure 1:** AKC and ROP findings of a patient in Group-1. (A) Eyelid swelling, mild corneal edema, conjunctival injection and intense chemosis due to AKC; (B) the appearance of ROP findings in the fundus.

AKC: Adenoviral keratoconjunctivitis, ROP: Retinopathy of prematurity

**Table 1:** Demographic characteristics and some clinical findings in the 2 groups

*Chi-Square test and Mann-Whiney U test

Table 1: Demographic characteristics and some clinical findings in groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (18 eyes, ROP with AKC)</th>
<th>Group 2 (26 eyes, ROP without AKC)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA at birth, weeks</td>
<td>27.6±2.6</td>
<td>28.3±3.0</td>
<td>0.427</td>
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<tr>
<td>Gender, F/M</td>
<td>4/5</td>
<td>7/6</td>
<td>0.802</td>
</tr>
<tr>
<td>BW, grams</td>
<td>1168±383.0</td>
<td>1163±443.9</td>
<td>0.848</td>
</tr>
<tr>
<td>PCA at treatment</td>
<td>35.4±1.2</td>
<td>35.3±1.8</td>
<td>0.772</td>
</tr>
<tr>
<td>IVR / IVA</td>
<td>12/6</td>
<td>18/8</td>
<td>0.858</td>
</tr>
<tr>
<td>Presence of any postoperative complication (%)</td>
<td>0(0%)</td>
<td>0(0%)</td>
<td>-</td>
</tr>
<tr>
<td>Presence of rubeosisiridis (%)</td>
<td>5(27.8%)</td>
<td>10(34.1%)</td>
<td>0.461</td>
</tr>
<tr>
<td>Presence of reactivation of disease (%)</td>
<td>6(33.3%)</td>
<td>10(38.5%)</td>
<td>0.728</td>
</tr>
<tr>
<td>Additional treatment for reactivation</td>
<td>IVR for 3 eyes</td>
<td>LPC for 2 eyes</td>
<td>0.055</td>
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<tr>
<td>Presence of peripheral avascular area at last visit</td>
<td>5(27.8%)</td>
<td>4(15.4%)</td>
<td>0.316</td>
</tr>
</tbody>
</table>

*Chi-Square test and Mann-Whiney U test

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