RECURRENCE OF RETINOPATHY OF PREMATURITY AFTER INTRAVITREAL AFLIBERCEPT: A RETROSPECTIVE ANALYSIS

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Submitted 10November 2024; accepted 13 February 2025

ABSTRACT

Background: Retinopathy of Prematurity (R.O.P) is a primary cause of blindness in premature babies with abnormal retinal vasculature. Anti-VEGF agents, such as Aflibercept (Eylea), have also emerged as a treatment option for severe R.O.P instead of laser photocoagulation. The current study was conducted to evaluate the rate of recurrence of R.O.P following intravitreal Aflibercept injections in premature infants and the outcomes of re-treatment, including laser therapy.

Methods: A retrospective cohort study was conducted at Duhok Eye Hospital from 2019 to 2024. Participants included neonates treated with intravitreal Aflibercept injections for Type 1 R.O.P. Recurrent lesions were managed with additional Aflibercept injections, or in cases of peripheral recurrence, with laser therapy.

Results: A total of 122 eyes from preterm infants were treated with Aflibercept. R.O.P recurred in 51.6% of cases (63 eyes), with higher recurrence rates in zone 2 (58.8%) compared to Zone 1 (15%) ($p = 0.003$). All Zone 1 recurrences were successfully treated with additional Aflibercept injections. For Zone 2 recurrences, laser therapy was used, with 20% of cases requiring a second session. Complete retinal vascularization was achieved in 43.4% of eyes by 65 weeks postmenstrual age. No cases of endophthalmitis or vitreous hemorrhage were observed.

Conclusion: Aflibercept is an effective and safe treatment for Type 1 R.O.P, particularly in Zone 1. However, the higher rate of recurrence in Zone 2 mandates close follow-up and the potential role of adjunctive laser therapy.

Duhok Med J 2025; 19 (1): 71-79.

Keywords: Retinopathy of Prematurity; Aflibercept injections; laser therapy.

Over-all Retinopathy of Prematurity (R.O.P) is now identified as the most important single cause of visual loss and blindness in premature children worldwide. It is caused mainly by abnormal formation of retinal blood vessels resulting from the incomplete development of the retinal vasculature at the time of birth. The disease tends to show itself in two stages, the first stage resulting in mild cases being self-limiting and more severe cases needing medical intervention. Severe R.O.P can progress to retinal detachment and blindness if not corrected. The incidence of R.O.P as a public health problem has increased with the survival rates of preterm neonates due to improved neonatal care[1,2].

Laser photocoagulation has traditionally been the treatment of choice, mainly for cases with severe R.O.P. Although laser photocoagulation can efficiently stop disease progression, it unfortunately leads to the disruption of peripheral retinal tissue, causing peripheral vision loss and affecting retinal functions. Therefore, there is continued interest in alternative therapies that may minimize retinal toxicity while effectively halting disease progression[3,4].

The utilization of anti-VEGF agents, including Bevacizumab and Ranibizumab, has drastically transformed the therapeutic approaches for R.O.P by focusing on

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vascular endothelial growth factor (VEGF), a crucial protein that mediates abnormal angiogenesis in R.O.P. Clinical studies have demonstrated that these medications can effectively halt disease progression with less retinal damage than laser therapy. Most recently, intravitreal Aflibercept (Eylea), a very promising potent anti-VEGF agent, has gained FDA approval for the treatment of R.O.P, presenting clinicians with a novel tool to address this challenging condition (1). Whereas other anti-VEGF agents only inhibit VEGF-A, Aflibercept has the ability to target both VEGF-A and placental growth factor (PlGF), providing a more comprehensive mechanism of action[5-7].

While recent studies have shown Aflibercept's potential to slow R.O.P's progression in infants, leading to improved structural outcomes and fewer complications than traditional therapies, relapse following treatment has surfaced in multiple investigations, often affecting Zone 2. This underscores follow-up's critical nature and possibly requiring reapplying laser photocoagulation or supplemental anti-VEGF injections to address recurrences.

Comparisons of Bevacizumab and Ranibizumab may indicate Aflibercept provides longer duration, yet recurrence persists as a problem. In Sukgen et al.'s study, Aflibercept saw reoccurring R.O.P in many patients, especially Zone 2 cases. This prompts questions about optimal dosing frequency and whether a solitary drug can adequately prevent relapse.

The aim of this research is to evaluate R.O.P recurrence rates in premature babies receiving intravitreal Aflibercept at Duhok Eye Hospital from 2019 to 2024. Such information is important for long-term monitoring, and results on laser photocoagulation's efficacy as secondary therapy will prove valuable in managing strategies and halting recurrence.

PATIENTS AND METHODS:

This is a retrospective observational cohort analysis carried out at Duhok Eye Hospital from 2019 to 2024. The study aimed to evaluate recurrence rates in R.O.P after treatment with intravitreal Aflibercept (Eylea) among premature infants. Demographic data, clinical presentation, treatment characteristics, and outcomes of neonates diagnosed with Type 1 R.O.P were abstracted by chart review.

Eligible neonates were selected based on specific inclusion and exclusion criteria. Participants were all preterm infants born between 24-30 weeks gestational age, with a birth weight of 600–1600 grams, while infants with previous ocular treatments for R.O.P (e.g., laser photocoagulation, intravitreal injections of other anti-VEGF agents) were excluded from the current study.

Diagnosis for Type I R.O.P was done according to the International Classification of Retinopathy of Prematurity (ICROP) guidelines, which classify the severity and zones of disease involvement. Infants diagnosed with Type 1 R.O.P who need treatment and defined as: Zone I, any stage with plus disease or stage 3 with or without plus disease; Zone II, stage 2 or 3 with plus disease and while with Type II: Zone 1: Stage 1 or 2 without plus disease and Zone 2: stage 3 without plus disease.

Additional diseases include presence of other major ocular pathologies (e.g., congenital retinal diseases or ocular trauma) or with systemic conditions (e.g., severe sepsis, neurodevelopmental disorders) that might affect study outcomes[1].

Eligible infants underwent a complete ophthalmological evaluation, which included pupil dilation using phenylephrine 0.5–1% and tR.O.Picamide 1% dR.O.Ps. Fundus examination was performed with a 20D or 30D condensing lens after administering tetracaine eye dR.O.Ps for topical anesthesia. Eligible

infants received an intravitreal Aflibercept (1 mg/0.025 ml) injection under aseptic conditions. The injection was administered 1–1.5 mm posterior to the limbus using a 30-gauge needle after prepping the injection site with 5% iodine solution. Then infants were monitored with ocular exams on day 1 and days 5–6 post-treatment. To prevent infection, topical antibiotics were applied four times daily for 5 days. Follow-up ophthalmoscopies were performed every 6 weeks to check for recurrence that were defined as the reappearance of R.O.P requiring additional treatment[2].

Zone 1 recurrences were treated with additional intravitreal Aflibercept injections, while Zone 2 recurrences were managed with pan-retinal photocoagulation (PRP) using argon or infrared laser under general anesthesia. If retinal vascularization was not achieved by 65 weeks postmenstrual age, additional PRP sessions were performed[3].

All patients were assessed for the primary outcome, the recurrence rate of R.O.P after initial Aflibercept treatment; effectiveness of secondary treatments (e.g., repeat injections, laser therapy); time to recurrence (days from the initial injection to the recurrence) and occurrence of complications such as endophthalmitis, vitreous hemorrhage, or traumatic cataract[4].

After collection of data, the data were analyzed using SPSS software (version X), with descriptive statistics summarizing baseline characteristics and outcomes. Continuous variables were presented as means with standard deviations, and categorical variables as frequencies and percentages. Chi-square tests were used to compare recurrence rates between Zones 1 and 2, with p-values < 0.05 considered statistically significant.

RESULTS:

From the 2019–2024 period, a total of 122 eyes from preterm infants diagnosed with Type 1 R.O.P were studied. These neonates were treated with intravitreal Aflibercept at Duhok Eye Hospital. The cohort had a median gestational age of 26 weeks (range: 24–30 weeks) and an average birth weight of 1100 grams (range: 600–1600 grams). The study population was divided into two categories, eyes with R.O.P in Zone 1 and Zone 2, for comparison.

Overall (Table 1), 51.6% (63/122) of treated eyes experienced a recurrence of R.O.P following the initial Aflibercept injection. Notably, the recurrence rate was significantly higher in Zone 2 compared to Zone 1, with Zone 2: 58.8% recurrence (60 out of 102 eyes) and Zone 1: 15% recurrence (3 out of 20 eyes). The difference in recurrence rates between Zone 1 and Zone 2 was statistically significant ($p = 0.003$).

In Zone 1, all three recurrences were successfully treated with a second intravitreal Aflibercept injection, achieving complete retinal vascularization without requiring additional interventions. In Zone 2, all 60 recurrences were treated with PRP. Of these, 12 eyes (20%) required a second PRP session to achieve full disease control. The success rate of PRP in Zone 2 was 86.7% (52/60 eyes), resulting in complete retinal vascularization.

By 65 weeks postmenstrual age, 43.4% (53/122 eyes) of treated eyes achieved complete retinal vascularization. However, 6 eyes (4.9%) still exhibited incomplete retinal vascularization and required additional interventions, primarily PRP. There was no statistically significant difference in vascularization outcomes between eyes that experienced recurrence in Zone 1 and those in Zone 2 ($p = 0.14$).

No cases of severe ocular complications, such as endophthalmitis, vitreous hemorrhage, or traumatic cataract, were observed, resulting in a 0% complication

rate. Additionally, no statistically significant difference in complication rates was noted between eyes that experienced recurrence and those that did not (p = 1.00).

Table 1: Outcomes of Retinopathy of Prematurity (R.O.P), After Aflibercept Treatment by Zone

Outcome	Zone 1 (n)	Zone 2 (n)	Total		p-value
			(n)	%	
Total Eyes Treated	20	102	122	100	-
Recurrence Rate	3	60	63	51.6	0.003
Eyes Achieving Complete Vascularization	17	42	59	48.4	0.14
Eyes with Incomplete Vascularization at 65 Weeks	2	4	6	4.9	0.14
Eyes Treated with Additional Injection (Zone 1)	3	-	3	2.5	-
Eyes Treated with Laser Therapy (Zone 2)	-	60	60	49.2	-
Eyes Requiring Additional Laser Session (Zone 2)	-	12	12	9.8	-
Complications (Endophthalmitis)	0	0	0	0	1.00
Complications (Vitreous Hemorrhage)	0	0	0	0	1.00
Complications (Traumatic Cataract)	0	0	0	0	1.00

DISCUSSION

The introduction of anti-VEGF therapy has markedly revolutionized the management of R.O.P providing a viable alternative to traditional laser photocoagulation. This study offers valuable insights into the recurrence rates of R.O.P following intravitreal Aflibercept administration, highlighting its effectiveness, particularly in Zone 1, while emphasizing the challenges in managing Zone 2 disease[5]. Our findings not only reinforce the role of Aflibercept but also raise key considerations for optimizing treatment strategies to mitigate recurrence, especially in the peripheral retina

In our study, the overall recurrence level was 51.6%, which fits along with formerly noted biomimetic models of anti-VEGF solutions (38–57%)[2]. Nevertheless, the significantly higher rate of recurrence in Zone 2 (58.8%) than Zone 1 (15%) (p = 0.003) needs to be further explored. Above results are congruent with the literature as well[10,11], Sukgen et al has been claimed recurrence rates increase following anti-VEGF therapy in Zone 2[10].

Anatomical differences between Zone 1 and Zone 2 likely contribute to the disparity in recurrence rates. Zone 1, being centrally located, has a denser vascular network, which may respond more favorably to VEGF inhibition. In contrast, Zone 2, encompassing the peripheral retina, is more prone to incomplete vascular development even after VEGF suppression[7]. This suggests that while Aflibercept effectively halts disease progression in Zone 1, its efficacy in Zone 2 may be limited due to the more extensive area requiring vascularization. Furthermore, the rapid regrowth of vasculature in the peripheral retina may contribute to a higher likelihood of reactivation, underscoring the need for prolonged follow-up in Zone 2 cases.

The significantly higher recurrence rates in Zone 2 highlight the need for a tailored

therapeutic approach for this region. Our findings suggest that Aflibercept alone may not suffice to achieve sustained retinal vascularization in Zone 2, necessitating adjunctive treatments such as PRP. Notably, all Zone 2 recurrences in our cohort required PRP, with 20% of these cases requiring a second laser session to attain complete vascularization. These results are in line with prior reports indicating that laser therapy remains essential for preventing retinal detachment in Zone 2 R.O.P, despite the benefits conferred by anti-VEGF therapy[5,8,12-14].

Moreover, the high recurrence rate in Zone 2 raises the question of whether the dosing schedule and frequency of Aflibercept should be reconsidered for these patients. While Aflibercept's longer half-life compared to other agents such as Ranibizumab[7] is advantageous, its capacity to fully suppress VEGF-driven angiogenesis in peripheral retinal regions over time may be inadequate. Future studies should investigate whether modifications in injection timing or combining anti-VEGF agents with early laser therapy could reduce recurrence rates and improve long-term retinal outcomes in Zone 2.

In this study, Zone 1 recurrences were successfully managed with additional intravitreal Aflibercept injections, with all cases achieving complete retinal vascularization. This supports the hypothesis that Aflibercept's broader inhibition of both VEGF-A and placental growth factor (PlGF) may contribute to its superior efficacy in central retinal disease, compared to other anti-VEGF agents that primarily target VEGF-A alone[7,13]. These findings suggest that Aflibercept can provide sustained disease control in Zone 1, minimizing the need for more invasive interventions, such as laser photocoagulation.

Conversely, the need for laser therapy in Zone 2 recurrences underscores the limitations of anti-VEGF monotherapy in managing peripheral R.O.P. Although Aflibercept shows promise as a first-line treatment, all Zone 2 recurrences in this study required PRP, and 20% necessitated a second session to fully stabilize the retina. This observation is consistent with growing evidence suggesting that combination therapy—initial anti-VEGF treatment followed by laser photocoagulation—may be necessary to prevent disease progression in peripheral R.O.P[5,14].

When compared to other anti-VEGF agents such as Bevacizumab and Ranibizumab, Aflibercept appears to offer several advantages, particularly in its broader mechanism of action. Aflibercept's dual inhibition of VEGF-A and PlGF may provide a more comprehensive blockade of angiogenic pathways, which could explain its efficacy in reducing the progression of central R.O.P[1,7]. However, our study found that recurrence rates in Zone 2 following Aflibercept treatment were similar to those observed with Bevacizumab and Ranibizumab in other studies[5,9,14]. This raises the question of whether Aflibercept offers a true advantage in treating peripheral R.O.P or if its benefits are primarily confined to Zone 1 disease.

Ranibizumab, with its shorter half-life, may require more frequent dosing but could allow for more flexible management of VEGF levels over time[4]. Bevacizumab, although effective in peripheral R.O.P, raises concerns regarding systemic absorption and potential long-term side effects[3,5,15]. Head-to-head comparative studies between these agents are needed to determine the optimal treatment strategies for different zones of R.O.P.

A notable strength of our study is the absence of severe ocular complications, such as endophthalmitis, vitreous hemorrhage, or traumatic cataract, following intravitreal Aflibercept injections. This is consistent with the safety profile reported in previous studies

on Aflibercept in R.O.P[7,10,16]. Additionally, none of the infants in our cohort exhibited systemic complications related to neurodevelopment, addressing some concerns regarding the systemic safety of anti-VEGF agents in neonates[10,17,18,19].

Nonetheless, the long-term safety of anti-VEGF agents, particularly concerning neurodevelopmental outcomes, remains an area of ongoing research. Some studies have suggested potential risks of delayed neurodevelopment following anti-VEGF treatment, though the evidence remains inconclusive[16,18,20]. Therefore, while Aflibercept appears safe in the short term, extended follow-up is crucial to fully assess the potential systemic effects of VEGF inhibition in this vulnerable population

This study has several limitations. First, its retrospective design introduces the potential for selection bias and limits control over confounding factors. Second, while the follow-up period was adequate for detecting early recurrences, longer-term follow-up is necessary to fully assess the durability of Aflibercept treatment and the risk of late-onset recurrences. Finally, this was a single-center study, which may limit the generalizability of the findings. Larger, multicenter randomized trials are needed to provide more robust data on the comparative efficacy and safety of Aflibercept versus other anti-VEGF agents.

CONCLUSION:

Intravitreal Aflibercept (Eylea) is an effective choice for managing Type 1 R.O.P, particularly in Zone 1, showing lower recurrence rates and achieving near-total vascularization in most cases. Recurrence rates in Zone 2 remain a significant challenge, with many eyes requiring adjunctive treatments, including laser therapy. Aflibercept is well tolerated, with no major ocular complications observed.

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پوختە

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پێشەکی و ئارمانج: ....

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