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Comparative efficacy and safety of intravitreal anti-VEGF therapy versus laser photocoagulation in treatment--requiring retinopathy of prematurity

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HIGHLIGHTS

Anti-VEGF and laser are complementary in ROP; choice depends on clinical context, balancing efficacy, safety, and follow-up reliability.

ABSTRACT

Retinopathy of prematurity (ROP) remains a leading cause of preventable childhood blindness worldwide. While laser photocoagulation has long been the standard treatment, intravitreal anti-VEGF therapy is increasingly used, particularly for posterior disease. This narrative review integrates data from randomized trials, systematic reviews, and contemporary cohort studies to compare treatment efficacy, recurrence behavior, refractive outcomes, and systemic safety. Anti-VEGF therapy yields comparable regression rates, a lower risk of structural complications, and more favorable refractive outcomes. However, it is associated with a higher risk of reactivation and longer follow-up requirements. Anti-VEGF therapy is now widely favored for zone I and aggressive ROP, while laser remains essential when follow-up reliability is uncertain.

Key words: anti-VEGF, laser photocoagulation, retinopathy of prematurity

INTRODUCTION

Retinopathy of prematurity (ROP) continues to present a difficult clinical balance. The goal is not only to suppress abnormal vascular proliferation but also to preserve long-term visual function and minimize systemic risk in a fragile neonatal population. With improved survival of extremely premature infants, the global burden of ROP has risen, particularly in middle-income settings [1]. Historically, peripheral retinal ablation was the cornerstone of treatment, and the ETROP (Early Treatment for Retinopathy Of Prematurity) study confirmed that early treatment of high-risk disease improves outcomes [2]. The introduction of intravitreal anti-VEGF (vascular endothelial growth factor) therapy changed this paradigm. Rather than eliminating ischemic retina to reduce VEGF production, anti-VEGF therapy directly blocks the molecular driver of neovascularization [3].

LITERATURE REVIEW

Pathophysiology and therapeutic rationale

ROP develops through a biphasic process. After premature birth, relative hyperoxia suppresses VEGF and halts vascular growth. As metabolic demand increases, retinal hypoxia triggers a surge in angiogenic mediators, resulting in pathological neovascularization [4]. Laser photocoagulation reduces VEGF indirectly by destroying the avascular retina. Anti-VEGF therapy, by neutralizing VEGF directly, may allow continued physiologic vascularization toward the ora serrata [3]. Pharmacologic differences between agents influence both efficacy and recurrence behavior [5].

TABLE 1

Anti-VEGF agents used in ROP.

Agent	Molecular structure	Approximate weight	Target ligands
Bevacizumab [6]	full monoclonal antibody	~14 kDa	VEGF-A
Ranibizumab [6]	antibody fragment	~4 kDa	VEGF-A
Aflibercept [5]	fusion protein trap	~11 kDa	VEGF-A, VEGF-B, PlGF
Conbercept [3]	fusion protein trap	~14 kDa	VEGF-A, VEGF-B, PlGF

PlGF – placental growth factor; VEGF – vascular endothelial growth factor.

Primary treatment efficacy

The BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) trial first demonstrated the superiority of bevacizumab in zone I disease [2]. Subsequent trials, including RAINBOW (Randomized, Controlled Study Evaluating the Efficacy and Safety of RAnibizumab Compared With Laser Therapy for the Treatment of INfants BOrn Prematurely With Retinopathy of Prematurity) and FIREFLEYE, showed that ranibizumab and aflibercept achieved success rates broadly comparable to laser [7, 8]. A recurring theme across studies is that modern laser therapy performs extremely well. This strong performance makes demonstrating statistical superiority for newer therapies difficult, even when clinical differences appear meaningful.

TABLE 2

Major clinical trials comparing anti-VEGF therapy and laser therapy.

Trial	Drug	Drug success rate	Laser success rate	Primary endpoint
BEAT-ROP [5]	bevacizumab	superior in zone I (recurrence 6%)	inferior in zone I (recurrence 42%)	recurrence before 54 weeks PMA
RAINBOW [6]	ranibizumab	80%	66.2%	success at week 24
FIREFLEYE [5, 6]	aflibercept	85.5%	82.1%	week-24 success
BUTTERFLEYE [5–8]	aflibercept	79.6%	77%	week-52 success

PMA – postmenstrual age.

Structural outcomes

Several large, pooled analyses suggest that anti-VEGF therapy reduces the risk of retinal detachment and the need for salvage surgery compared with laser [1]. This advantage likely reflects preservation of the peripheral retina rather than its ablation. The difference may be particularly relevant in posterior disease, where laser would otherwise be extensive.

Reactivation and retreatment

The major limitation of anti-VEGF therapy is not early failure but late reactivation. Unlike lasers, which often produce a more definitive response, injected eyes may reactivate months later [6]. Ranibizumab tends to reactivate earlier due to rapid systemic clearance, whereas bevacizumab may show delayed recurrence. Aflibercept appears intermediate [5].

TABLE 3

Relative retreatment risk compared with laser [3].

Treatment	Relative retreatment risk	Mean time to retreatment
Laser	reference	-
Bevacizumab	lower–moderate	~11 week
Ranibizumab	highest	~9 weeks
Aflibercept	intermediate	~1 weeks

Because of this delayed reactivation profile, infants treated with anti-VEGF often require follow-up until 6–10 weeks PMA (postmenstrual age) [4, 5, 8].

Refractive development

Laser treatment is known to influence ocular growth patterns and has long been associated with an increased risk of myopia. Eyes that undergo laser ablation frequently exhibit structural characteristics, including steeper corneal curvature, thicker crystalline lenses, and relatively shallow anterior chambers. In contrast, anti-VEGF therapy appears to allow ocular development to proceed more physiologically. As a result, several studies have reported a significantly lower incidence of high myopia in eyes treated with injections than in those treated with laser [9].

TABLE 4

Refractive outcomes after treatment anti-VEGF vs laser.

Parameter	Anti-VEGF therapy	Laser therapy
Mean spherical equivalent [5]	~0 D	-2.4 to -12 D
High myopia prevalence [3, 5, 6, 8]	0–35 %	20–51%
Peripheral visual field	preserved	reduced

Systemic safety

Systemic safety remains a primary concern when anti-VEGF therapy is used in neonates. Several observational studies have reported a higher mortality rate among infants receiving intravitreal injections, yet this finding has not been confirmed in randomized controlled trials [9]. This difference is most likely explained by confounding by indication. In clinical practice, injections are often chosen for infants who are already in a more unstable condition and may not tolerate the anesthesia required for laser treatment [3]. In addition, the extent of systemic VEGF suppression appears to differ between agents. Bevacizumab is generally associated with the longest duration of systemic suppression, ranibizumab with the shortest, and aflibercept with an intermediate profile [10].

Practical implementation

Laser photocoagulation is resource-intensive and usually requires anesthesia support. Anti-VEGF injections are shorter procedures and can be performed at the bedside [8]. However, the procedural simplicity of injections is offset by the prolonged post-injection surveillance period.

TABLE 5

Practical comparison of treatment approaches [5].

Feature	Laser photocoagulation	Anti-VEGF injection
Duration	1–2 h	<1 min
Anesthesia	required	topical possible
Setting	operating room	NICU bedside
Follow-up period	finite	extended

NICU – neonatal intensive care unit.

DISCUSSION

The comparison between laser photocoagulation and anti-VEGF therapy in ROP is often framed as a competition between an established surgical standard and a newer pharmacologic alternative. However, the evidence increasingly suggests that this is a false dichotomy. The two approaches differ not only in mechanism but in the type of risk they redistribute across the infant's clinical course.

Laser therapy concentrates risk in the procedural phase. It requires anesthesia, has a longer treatment time, and imposes immediate physiological stress. Yet once successful, it tends to provide a stable and predictable outcome with relatively limited late recurrence. In contrast, anti-VEGF therapy shifts risk forward in time. The injection itself is brief and physiologically gentle. Still, it introduces prolonged uncertainty regarding vascular maturation and potential reactivation, with delayed reactivation requiring prolonged surveillance, particularly in zone II disease [11–15].

This temporal redistribution of risk may explain why the choice of therapy often varies more by clinical context than by efficacy alone. In tertiary centers with reliable follow-up infrastructure, anti-VEGF therapy may be favored because its refractive and anatomical advantages become clinically meaningful over time. In contrast, in settings where follow-up adherence is uncertain, the predictability of laser may outweigh its refractive disadvantages [13, 14, 16, 17].

Another recurring issue in the literature is the interpretation of systemic safety signals. Observational datasets frequently suggest higher mortality in anti-VEGF-treated infants, yet randomized trials consistently fail to replicate this finding. This discrepancy highlights a classic epidemiological challenge: treatment allocation in clinical practice is rarely random. Infants selected for injection often represent a higher-risk subgroup, and without careful adjustment, outcome differences may reflect baseline morbidity rather than drug toxicity [9, 13, 17, 18].

From a functional perspective, refractive outcome may represent one of the most clinically meaningful distinctions between treatments. While structural success remains the immediate priority, the long-term visual burden of high myopia should not be underestimated. If anti-VEGF therapy consistently reduces severe refractive sequelae, its benefits may extend well beyond infancy [19–21].

Taken together, the current evidence suggests that treatment selection in ROP should not be framed as choosing the better therapy in absolute terms. Rather, it should be viewed as aligning the disease's biological behavior with the logistical realities of the clinical environment. This perspective may help reconcile the seemingly contradictory findings across trials and observational studies [9, 11, 22].

CONCLUSIONS

Laser photocoagulation and anti-VEGF therapy should not be positioned as opposing treatment options, but rather as approaches that can complement each other depending on the clinical situation. Anti-VEGF therapy tends to be more advantageous in posterior disease, is associated with more favorable refractive development, and generally imposes less procedural stress on the infant. Nevertheless, laser treatment remains important, particularly in settings where long-term follow-up cannot be reliably ensured. Research efforts may benefit from shifting away from simply comparing which treatment is superior overall. Instead, greater emphasis should be placed on identifying patient-specific characteristics that influence treatment response, thereby enabling more precise tailoring of therapeutic decisions to each infant's clinical profile.

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