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TREATMENT OF RETINOPATHY OF PREMATURITY AND LONG-TERM NEUROVISUAL DEVELOPMENT

TRATAMENTO DA RETINOPATIA DA PREMATURIDADE E DESENVOLVIMENTO NEUROVISUAL EM LONGO PRAZO

TRATAMIENTO DE LA RETINOPATÍA DEL PREMATURO Y DESARROLLO NEUROVISUAL A LARGO PLAZO

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ABSTRACT

Introduction: Retinopathy of prematurity develops during a period in which retinal vascularization, ocular growth, and maturation of the cerebral visual system occur simultaneously. Laser photocoagulation provides durable disease control by ablating avascular retina, whereas intravitreal anti–vascular endothelial growth factor therapy preserves peripheral retina but can delay vascular maturation and permit late reactivation. Treatment must therefore be evaluated beyond initial regression by considering retinal integrity, refractive development, visual function, and neurodevelopment.

Objective: To critically synthesize the long-term ocular and neurodevelopmental outcomes associated with laser photocoagulation, bevacizumab, ranibizumab, aflibercept, and vitreoretinal surgery for retinopathy of prematurity, emphasizing quantitative comparative evidence and clinically relevant surveillance.

Methods: A structured narrative review of PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library was conducted. Randomized trials, planned trial extensions, comparative cohorts, systematic reviews, and meta-analyses reporting structural success, recurrence, retinal detachment, refractive error, visual acuity, strabismus, cerebral palsy, developmental scores, or composite neurodevelopmental impairment were prioritized. Treatment effects were interpreted separately from the consequences of extreme prematurity and retinopathy severity.

Results and Discussion: Earlier retinal ablation for type 1 retinopathy of prematurity reduced unfavorable visual and structural outcomes compared with treatment delayed until conventional threshold disease. In the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity trial, recurrence requiring retreatment occurred in 4% of bevacizumab-treated eyes and 22% of laser-treated eyes, predominantly because of the benefit observed in zone I disease. Very high myopia at approximately 2.5 years was

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substantially less frequent after bevacizumab. The Ranibizumab Compared With Laser Therapy for the Treatment of Infants Born Prematurely With Retinopathy of Prematurity trial found 24-week treatment success rates of 80% with ranibizumab 0.2 mg and 66% with laser. At five years, visual acuity was similar, while high myopia remained less frequent after ranibizumab. FIREFLEYE and FIREFLEYE next demonstrated durable anatomical control with aflibercept through three years and a lower frequency of high myopia than with laser, although the original trial did not satisfy its prespecified noninferiority criterion. A meta-analysis including 10,516 infants associated anti-vascular endothelial growth factor therapy with lower risks of retinal detachment, surgery, and myopia and found no pooled difference in neurodevelopment. Observational mortality signals were not reproduced in randomized trials. Neurodevelopmental comparisons remain vulnerable to confounding by illness severity and are underpowered to identify small treatment effects.

Conclusion: Treatment selection should be individualized according to disease zone and severity, systemic stability, capacity for prolonged follow-up, and family circumstances. Anti–vascular endothelial growth factor therapy provides major refractive and retinal-preservation advantages, particularly for posterior disease, but transfers part of the treatment burden from the initial procedure to several months of surveillance. Current evidence does not establish a clinically important treatment-specific neurodevelopmental disadvantage, but neither does it exclude small or late effects. Long-term ophthalmological and developmental follow-up remains necessary regardless of the initial treatment modality.

Keywords: Retinopathy of Prematurity. Laser Photocoagulation. Vascular Endothelial Growth Factor Inhibitors. Visual Development. Neurodevelopment. Premature Infant.

RESUMO

Introdução: A retinopatia da prematuridade se desenvolve durante um período em que a vascularização da retina, o crescimento ocular e a maturação do sistema visual cerebral ocorrem simultaneamente. A fotocoagulação a laser proporciona controle duradouro da doença por meio da ablação da retina avascular, enquanto a terapia intravítrea com agentes antiangiogênicos do fator de crescimento endotelial vascular preserva a retina periférica, mas pode retardar a maturação vascular e permitir a reativação tardia. Portanto, o tratamento deve ser avaliado para além da regressão inicial da doença, considerando a integridade da retina, o desenvolvimento refracional, a função visual e o desenvolvimento neurológico.

Objetivo: Sintetizar criticamente os resultados oculares e do desenvolvimento neurológico em longo prazo associados à fotocoagulação a laser, ao bevacizumabe, ao ranibizumabe, ao aflibercepte e à cirurgia vitreorretiniana para o tratamento da retinopatia da prematuridade, enfatizando evidências comparativas quantitativas e estratégias de acompanhamento clinicamente relevantes.

Métodos: Foi realizada uma revisão narrativa estruturada nas bases PubMed/MEDLINE, Scopus, Web of Science e Cochrane Library. Foram priorizados ensaios clínicos randomizados, extensões planejadas de ensaios, coortes comparativas, revisões sistemáticas e metanálises que apresentassem dados sobre sucesso estrutural, recorrência, descolamento de retina, erro refrativo, acuidade visual, estrabismo, paralisia cerebral, escores de desenvolvimento ou comprometimento do desenvolvimento neurológico composto. Os efeitos do tratamento foram interpretados separadamente das consequências da prematuridade extrema e da gravidade da retinopatia.

Resultados e Discussão: A ablação retiniana mais precoce para a retinopatia da prematuridade do tipo 1 reduziu os resultados visuais e estruturais desfavoráveis em comparação com o tratamento adiado até o estágio convencional de doença limiar. No estudo Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity, a recorrência que exigiu retratamento ocorreu em 4% dos olhos tratados com bevacizumabe e em 22% dos olhos tratados com laser, principalmente devido ao benefício observado na doença em zona I. A miopia muito elevada aos aproximadamente 2,5 anos de idade foi substancialmente menos frequente após o tratamento com bevacizumabe. O estudo Ranibizumab Compared With Laser Therapy for the Treatment of Infants Born Prematurely With Retinopathy of Prematurity encontrou taxas de sucesso terapêutico em 24 semanas de 80% com ranibizumabe 0,2 mg e 66% com laser. Aos cinco anos, a acuidade visual foi semelhante, enquanto a miopia elevada permaneceu menos frequente após o ranibizumabe. Os estudos FIREFLEYE e FIREFLEYE next demonstraram controle anatômico duradouro com aflibercepte até três anos e menor frequência de miopia elevada em comparação com o laser, embora o estudo original não tenha atendido ao critério de não inferioridade previamente especificado. Uma metanálise que incluiu 10.516 crianças associou a terapia antiangiogênica do fator de crescimento endotelial vascular a menores riscos de descolamento de retina, cirurgia e miopia, não tendo encontrado diferença agrupada no desenvolvimento neurológico. Sinais de mortalidade observados em estudos observacionais não foram reproduzidos em ensaios randomizados. As comparações do desenvolvimento neurológico permanecem vulneráveis ao confundimento pela gravidade clínica e apresentam poder estatístico insuficiente para identificar pequenos efeitos do tratamento.

Conclusão: A escolha do tratamento deve ser individualizada de acordo com a zona e a gravidade da doença, a estabilidade sistêmica, a capacidade de realizar acompanhamento prolongado e as circunstâncias familiares. A terapia antiangiogênica do fator de crescimento endotelial vascular oferece importantes vantagens refracionais e de preservação da retina, especialmente em casos de doença posterior, mas transfere parte da carga do tratamento do procedimento inicial para vários meses de acompanhamento. As evidências atuais não estabelecem uma desvantagem clinicamente importante específica do tratamento em relação ao desenvolvimento neurológico, mas também não excluem efeitos pequenos ou tardios. O acompanhamento oftalmológico e do desenvolvimento em longo prazo permanece necessário independentemente da modalidade de tratamento inicialmente utilizada.

Palavras-chave: Retinopatia da Prematuridade. Fotocoagulação a Laser. Inibidores do Fator de Crescimento Endotelial Vascular. Desenvolvimento Visual. Desenvolvimento Neurológico. Recém-Nascido Prematuro.

RESUMEN

Introducción: La retinopatía del prematuro se desarrolla durante un período en el que la vascularización de la retina, el crecimiento ocular y la maduración del sistema visual cerebral ocurren simultáneamente. La fotocoagulación con láser proporciona un control duradero de la enfermedad mediante la ablación de la retina avascular, mientras que la terapia intravítrea con agentes antiangiogénicos contra el factor de crecimiento endotelial vascular preserva la retina periférica, pero puede retrasar la maduración vascular y permitir una reactivación tardía. Por lo tanto, el tratamiento debe evaluarse más allá de la regresión inicial de la enfermedad, considerando la integridad de la retina, el desarrollo refractivo, la función visual y el desarrollo neurológico.

Objetivo: Sintetizar críticamente los resultados oculares y del desarrollo neurológico a largo plazo asociados con la fotocoagulación con láser, bevacizumab, ranibizumab, aflibercept y cirugía vitreorretiniana para la retinopatía del prematuro, haciendo hincapié en la evidencia comparativa cuantitativa y en estrategias de seguimiento clínicamente relevantes.

Métodos: Se realizó una revisión narrativa estructurada de PubMed/MEDLINE, Scopus, Web of Science y Cochrane Library. Se priorizaron ensayos clínicos aleatorizados, extensiones planificadas de ensayos, cohortes comparativas, revisiones sistemáticas y metanálisis que informaran sobre éxito estructural, recurrencia, desprendimiento de retina, error refractivo, agudeza visual, estrabismo, parálisis cerebral, puntuaciones del desarrollo o deterioro del desarrollo neurológico compuesto. Los efectos del tratamiento se interpretaron por separado de las consecuencias de la prematuridad extrema y de la gravedad de la retinopatía.

Resultados Y Discusión: La ablación retiniana más temprana para la retinopatía del prematuro de tipo 1 redujo los resultados visuales y estructurales desfavorables en comparación con el tratamiento retrasado hasta la enfermedad umbral convencional. En el estudio Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity, la recurrencia que requirió retratamiento ocurrió en el 4% de los ojos tratados con bevacizumab y en el 22% de los ojos tratados con láser, principalmente debido al beneficio observado en la enfermedad de zona I. La miopía muy elevada alrededor de los 2,5 años de edad fue sustancialmente menos frecuente después del tratamiento con bevacizumab. El estudio Ranibizumab Compared With Laser Therapy for the Treatment of Infants Born Prematurely With Retinopathy of Prematurity encontró tasas de éxito terapéutico a las 24 semanas del 80% con ranibizumab 0,2 mg y del 66% con láser. A los cinco años, la agudeza visual fue similar, mientras que la miopía elevada siguió siendo menos frecuente después del ranibizumab. Los estudios FIREFLEYE y FIREFLEYE next demostraron un control anatómico duradero con aflibercept hasta los tres años y una menor frecuencia de miopía elevada en comparación con el láser, aunque el estudio original no cumplió con el criterio de no inferioridad previamente establecido. Un metanálisis que incluyó a 10.516 niños asoció la terapia antiangiogénica contra el factor de crecimiento endotelial vascular con menores riesgos de desprendimiento de retina, cirugía y miopía, y no encontró diferencias agrupadas en el desarrollo neurológico. Las señales de mortalidad observadas en estudios observacionales no se reprodujeron en ensayos aleatorizados. Las comparaciones del desarrollo neurológico siguen siendo vulnerables a la confusión derivada de la gravedad clínica y presentan una potencia estadística insuficiente para identificar pequeños efectos del tratamiento.

Conclusión: La elección del tratamiento debe individualizarse de acuerdo con la zona y la gravedad de la enfermedad, la estabilidad sistémica, la capacidad para realizar un seguimiento prolongado y las circunstancias familiares. La terapia antiangiogénica contra el factor de crecimiento endotelial vascular ofrece importantes ventajas refractivas y de preservación de la retina, especialmente en casos de enfermedad posterior, pero traslada parte de la carga del tratamiento desde el procedimiento inicial hacia varios meses de seguimiento. La evidencia actual no establece una desventaja clínicamente importante específica del tratamiento en relación con el desarrollo neurológico, pero tampoco excluye efectos pequeños o tardíos. El seguimiento oftalmológico y del desarrollo a largo plazo sigue siendo necesario independientemente de la modalidad de tratamiento inicial.

Palabras clave: Retinopatía del Prematuro. Fotocoagulación con Láser. Inhibidores del Factor de Crecimiento Endotelial Vascular. Desarrollo Visual. Desarrollo Neurológico. Recién Nacido Prematuro.

1 INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative retinal vascular disorder affecting preterm infants whose retinal vascularization remains incomplete. Its severity is described according to retinal zone, disease stage, extent, plus disease, and the presence of aggressive ROP under the International Classification of Retinopathy of Prematurity, Third Edition (ICROP3).[1]

ROP develops while the retinal vasculature, optic pathways, visual cortex, and higher-order visuospatial networks are undergoing rapid maturation. The clinically relevant outcome is consequently not limited to regression of plus disease. Treatment should also be evaluated according to durable retinal attachment, useful visual function, refractive development, binocular vision, and the neurodevelopmental potential permitted by the child's degree of prematurity.[1,2]

The burden of ROP is inseparable from advances in neonatal survival. Extremely preterm and extremely low-birth-weight infants have the greatest risk, although the population requiring screening varies among healthcare systems according to oxygen administration, neonatal resources, screening coverage, and survival of more mature preterm infants.[3]

ROP is simultaneously a retinal disease and a marker of cumulative neonatal vulnerability. Severe disease frequently coexists with bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, prolonged mechanical ventilation, growth failure, and lower gestational age. Each of these conditions is independently associated with unfavorable neurodevelopment.[3,4]

Comparisons between treatment modalities that inadequately measure these factors may therefore attribute developmental outcomes to ophthalmological treatment that were actually caused by baseline neonatal illness.

The therapeutic principle established by retinal ablation is the reduction of angiogenic stimulus originating from the peripheral avascular retina. Cryotherapy initially demonstrated that treatment could prevent progression to retinal detachment. Laser photocoagulation subsequently became the preferred ablative modality because it is more controllable and generally produces less inflammation.[5]

Laser photocoagulation has a long history of durable disease control, a relatively well-defined treatment endpoint, and a shorter high-risk interval for recurrence than pharmacological therapy. Its disadvantages include permanent ablation of peripheral retina, prolonged procedural and anesthesia exposure, possible visual-field restriction, and

significant myopic and anterior-segment remodeling, particularly when confluent treatment is required in posterior disease.[5]

Intravitreal anti–vascular endothelial growth factor (anti-VEGF) therapy changed ROP treatment by rapidly suppressing neovascular activity without destroying the peripheral retina. This characteristic is especially advantageous in zone I or aggressive posterior disease, in eyes with inadequate pupillary dilation or media opacity, and in systemically unstable infants for whom prolonged laser treatment may be undesirable.[5]

Bevacizumab, ranibizumab, and aflibercept differ in molecular structure, systemic persistence, VEGF-binding properties, regulatory approval, and evidence supporting specific neonatal doses. These agents should not be interpreted as completely interchangeable when systemic exposure, retinal vascularization, and reactivation are considered.[5]

The mechanism responsible for the ocular effectiveness of anti-VEGF therapy also generates systemic safety concerns. VEGF participates in the physiological development of the brain, lungs, kidneys, and other organs. Detectable systemic bevacizumab and prolonged suppression of circulating VEGF have been demonstrated after intravitreal injection in premature infants.[6,7]

The magnitude and duration of systemic VEGF suppression vary according to drug and dose. Pharmacokinetic plausibility does not independently prove neurodevelopmental harm, but it supports dose minimization, avoidance of unnecessary repeat exposure, and long-term evaluation of cognition, language, motor development, behavior, and sensory function.[6,7]

Long-term neurovisual development is multidimensional. It includes retinal attachment, macular structure, monocular and binocular visual acuity, refraction, accommodation, ocular alignment, stereopsis, amblyopia, peripheral visual field, contrast sensitivity, visual-motor integration, and cerebral visual function.[8]

A child may have an attached retina but remain visually impaired because of optic-nerve injury, macular displacement, high myopia, anisometropia, strabismus, amblyopia, nystagmus, or cerebral visual impairment. Conversely, a difference in developmental scores should not automatically be attributed to anti-VEGF exposure when treatment groups differ in gestational age, neurological injury, respiratory morbidity, socioeconomic characteristics, or treatment indication.[8]

The current evidence therefore requires a balanced interpretation. Acute disease regression is necessary but insufficient. Preservation of peripheral retina must be weighed

against delayed reactivation and the burden of surveillance. Refractive advantages must be distinguished from visual-acuity benefits, and systemic safety must be investigated with designs capable of controlling confounding by indication.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

To evaluate how treatment of ROP with laser photocoagulation, intravitreal anti-VEGF agents, or vitreoretinal surgery influences long-term neurovisual development, including retinal structure, visual function, refractive development, and neurodevelopment.

2.2 SECONDARY OBJECTIVES

1. To compare durable ROP control, recurrence or reactivation, retreatment, retinal detachment, and the requirement for vitreoretinal surgery among treatment modalities.
2. To quantify long-term differences in myopia, high myopia, visual acuity, strabismus, amblyopia, and other functional ocular outcomes.
3. To determine whether observational associations involving cognitive development, language, motor function, cerebral palsy, mortality, or composite neurodevelopmental impairment are supported by randomized and prospective evidence.
4. To distinguish treatment effects from the consequences of gestational age, systemic illness, neurological injury, ROP zone, disease severity, and treatment-selection bias.
5. To develop a practical surveillance framework following laser, anti-VEGF treatment, or vitreoretinal surgery and identify priorities for future research.

3 METHODOLOGY

3.1 REVIEW DESIGN AND INFORMATION SOURCES

A structured narrative review was conducted to integrate outcomes and follow-up periods that were too heterogeneous for a new quantitative synthesis. PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library were searched from database inception through August 2026.

Reference lists from pivotal randomized trials, systematic reviews, technology assessments, and long-term follow-up studies were examined to identify related publications from the same populations.

3.2 SEARCH CONCEPTS AND ELIGIBILITY CRITERIA

Search concepts included retinopathy of prematurity, laser photocoagulation, cryotherapy, anti-VEGF, bevacizumab, ranibizumab, aflibercept, vitrectomy, retinal detachment, recurrence, reactivation, visual acuity, myopia, strabismus, neurodevelopment, Bayley scales, cerebral palsy, and long-term follow-up.

Eligible evidence included randomized clinical trials, planned trial extensions, comparative prospective and retrospective cohorts, registry studies, systematic reviews, meta-analyses, and professional evidence assessments.

Studies limited to acute disease regression without interpretable structural, refractive, functional, or developmental follow-up were used only to contextualize longer-term outcomes.

3.3 OUTCOME FRAMEWORK

Outcomes were organized into four domains:

1. Ocular effectiveness: regression, recurrence or reactivation, retreatment, retinal detachment, and vitreoretinal surgery.
2. Ocular development: refractive error, axial and anterior-segment growth, visual acuity, ocular alignment, and amblyopia.
3. Neurological and developmental outcomes: cognitive, language, and motor scores, cerebral palsy, hearing impairment, blindness, composite neurodevelopmental impairment, and mortality.
4. Treatment burden: anesthesia exposure, procedural complexity, persistent avascular retina, retreatment, and duration of surveillance.

When both eyes were analyzed, the statistical unit and potential correlation between eyes were considered when interpreting statistical precision.

3.4 EVIDENCE APPRAISAL AND SYNTHESIS

Randomized allocation, masking of outcome assessment, completeness of follow-up, consistency of treatment definitions, prespecification of outcomes, and industry sponsorship were considered when evaluating trial evidence.

Observational studies were assessed according to confounding by indication, baseline neonatal illness, ROP zone and severity, institutional practice, changes in neonatal care over time, missing outcomes, and model overfitting.

Effect estimates with 95% confidence intervals were prioritized. Data derived from overlapping cohorts were not interpreted as independent replication.

Because agents, doses, disease zones, rescue criteria, and developmental instruments differed among studies, results were synthesized narratively. Published meta-analyses were used for pooled estimates.

Interpretive principle: A favorable retinal or refractive outcome following anti-VEGF therapy does not prove superior neurodevelopment. Similarly, an unfavorable developmental association in an observational cohort does not independently prove systemic drug toxicity. These questions require different designs, outcomes, and causal assumptions.

4 RESULTS

4.1 EVIDENCE BASE

The evidence was anchored by the Early Treatment for Retinopathy of Prematurity (ETROP) trial for the timing of retinal ablation; the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) trial and its refractive follow-up; the Ranibizumab Compared With Laser Therapy for the Treatment of Infants Born Prematurely With ROP (RAINBOW) trial and its two- and five-year extensions; and the Aflibercept for ROP Intravitreal Injection Versus Laser Therapy (FIREFLEYE) trial and prospective FIREFLEYE next follow-up.

Additional evidence included the Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in ROP (CARE-ROP) program, comparative neurodevelopmental cohorts, systematic reviews, meta-analyses, and an American Academy of Ophthalmology evidence assessment.

4.2 OVERALL FINDINGS

Four consistent patterns were identified.

First, timely treatment of type 1 ROP improves structural and visual prognosis compared with waiting for conventional threshold disease.

Second, anti-VEGF therapy is highly effective for posterior ROP and generally preserves a more favorable refractive trajectory than laser photocoagulation.

Third, pharmacological treatment has a distinct failure pattern. Initial regression may be followed by delayed reactivation or persistent avascular retina several weeks or months later. Consequently, loss to follow-up represents a greater risk after anti-VEGF therapy.

Fourth, the strongest available evidence does not demonstrate a consistent treatment-specific neurodevelopmental disadvantage. Nevertheless, randomized trials and their extensions remain insufficiently powered to exclude small differences, rare outcomes, or effects emerging later in childhood.

Table 1

Principal comparative studies of ocular efficacy and long-term visual outcomes

Study	Design and sample	Treatment comparison	Follow-up and outcome	Principal quantitative finding	Interpretation
ETROP, 2003 and 2010[9,10]	401 infants with high-risk prethreshold ROP	Earlier peripheral ablation versus conventional management until threshold disease	Nine months and six years; unfavorable vision and retinal structure	At nine months, unfavorable grating acuity: 14.5% versus 19.5%. At six years in type 1 eyes, unfavorable acuity: 25.1% versus 32.8%; unfavorable structure: 8.9% versus 15.2%	Type 1 ROP should be treated promptly; benefit should not be extrapolated to type 2 disease
BEAT-ROP, 2011[11]	150 infants and 300 eyes	Bevacizumab 0.625 mg versus laser for zone I or posterior zone II stage 3+ ROP	Recurrence requiring retreatment through 54 weeks' postmenstrual age	Recurrence: 4% versus 22%; benefit significant for zone I but not posterior zone II	Strong posterior-zone efficacy, but the trial was not powered for systemic safety
BEAT-ROP refractive follow-up, 2014[12]	109 infants and 211 eyes at approximately 2.5 years	Original bevacizumab versus laser allocation	Cycloplegic refraction and very high myopia	Zone I: 3.8% versus 51.4%; posterior zone II: 1.7% versus 36.4%	Large and clinically important refractive advantage after bevacizumab
RAINBOW, 2019[13]	225 randomized infants; 214 assessed at 24 weeks	Ranibizumab 0.2 mg, ranibizumab 0.1 mg, or laser	Survival without active ROP, unfavorable structure, or treatment switch	Success: 80%, 75%, and 66%, respectively; OR for 0.2 mg versus laser 2.19 (95% CI 0.99–4.82)	Results favored 0.2 mg, but the prespecified superiority threshold was narrowly missed
RAINBOW extension, 2024[16]	156 children assessed at five years	Original ranibizumab or laser allocation	Visual acuity, high myopia, and nonocular development	Better-eye letter score: 66.8, 64.6, and 62.1; high myopia in at least one eye: 8%, 15%, and 24%	Five-year acuity was similar, while the refractive advantage persisted
FIREFLEYE, 2022[17]	118 randomized infants; 113 treated	Aflibercept 0.4 mg versus laser	Treatment success at 24 weeks	Success: 85.5% versus 82.1%; prespecified noninferiority criterion not satisfied	Both groups had high success, but formal noninferiority cannot be claimed
FIREFLEYE next, 2024[18]	100 enrolled children; 95 assessed at two years	Prospective follow-up of aflibercept and laser groups	Structure, fixation, refraction, and development	No unfavorable structure: 93.9% versus 94.1%; high myopia: 7.8% versus 21.7%	Stable structure and less high myopia after aflibercept

Study	Design and sample	Treatment comparison	Follow-up and outcome	Principal quantitative finding	Interpretation
FIREFLEYE next, 2026[19]	90 children with three-year data	Aflibercept versus laser	ROP activity, visual acuity, refraction, and growth	No ROP: 98.3% versus 96.7%; visual acuity ≥20/40: 66.7% versus 47.8%; high myopia: 8.9% versus 24.1%	Durable control with descriptive visual and refractive advantages
Wang et al., 2026[27]	12 randomized trials and 58 observational studies; 10,516 infants	Any anti-VEGF therapy versus laser	Mortality, detachment, surgery, myopia, and neurodevelopment	Retinal detachment RR 0.36; surgery RR 0.38; myopia RR 0.67; neurodevelopment RR 1.05	Pooled ocular advantages; mortality signal was limited to observational studies

CI: confidence interval; OR: odds ratio; ROP: retinopathy of prematurity; RR: risk ratio.

5 RESULTS AND DISCUSSION

5.1 TIMELY RETINAL ABLATION AND DURABLE DISEASE CONTROL

The ETROP randomized trial established that treatment should be guided by the probability of an unfavorable outcome rather than postponed until conventional threshold disease. At approximately nine months, earlier treatment reduced unfavorable grating visual acuity from 19.5% to 14.5%. This corresponds to an absolute reduction of 5 percentage points and a relative reduction of approximately 26%.[9]

The visual benefit was accompanied by improved retinal structure and formed the basis of the current distinction between type 1 ROP, which requires prompt treatment, and type 2 ROP, which can generally be closely observed.[9]

The six-year ETROP findings are more informative for long-term neurovisual development. Across all high-risk prethreshold eyes, the difference in unfavorable visual acuity was not statistically significant. Under the prespecified clinical algorithm, however, unfavorable acuity occurred in 25.1% of early-treated type 1 eyes and 32.8% of conventionally managed eyes.[10]

Unfavorable retinal structure occurred in 8.9% and 15.2%, respectively. Type 2 eyes did not benefit from early ablation, and approximately 52% regressed without treatment.[10]

The relevant principle is not that every earlier intervention is beneficial. Treatment should be initiated when the expected visual and structural benefit exceeds the cost of ablating peripheral retina.

Laser remains a reference treatment because the ablated retina no longer sustains the same late angiogenic stimulus. When treatment is complete, the interval of high recurrence risk is comparatively finite and reactivation generally occurs earlier than after anti-VEGF therapy.

This durability is particularly valuable when reliable prolonged follow-up cannot be guaranteed. Laser also avoids systemic anti-VEGF exposure.

The tradeoff is permanent peripheral-retinal destruction, procedural or anesthesia burden, and a greater probability of treatment-associated myopia and anterior-segment alterations.

Laser is therefore not an obsolete comparator. It is a durable and effective treatment whose main long-term disadvantages are retinal and refractive, while anti-VEGF therapy preserves peripheral retina but requires a longer and less forgiving surveillance pathway.

5.2 ANTI-VEGF EFFICACY ACCORDING TO DISEASE ZONE, AGENT, DOSE, AND FOLLOW-UP

BEAT-ROP randomized 150 infants with bilateral zone I or posterior zone II stage 3+ disease. Recurrence requiring retreatment occurred in 6 of 140 bevacizumab-treated eyes and 32 of 146 laser-treated eyes. This represented an absolute reduction of approximately 17.6 percentage points.[11]

The treatment effect was significant for zone I disease but not for posterior zone II ROP. This interaction is clinically coherent because the more posterior the avascular retina, the greater the retinal cost and technical difficulty of complete laser treatment.

BEAT-ROP must nevertheless be interpreted according to its design. Its primary outcome was recurrence through 54 weeks' postmenstrual age rather than long-term visual acuity or neurodevelopment.

The sample was inadequate for identifying uncommon systemic adverse events. Bevacizumab was administered at half the adult intravitreal dose rather than at a dose established through neonatal dose-finding studies.[11]

Subsequent refractive follow-up answered an important question concerning ocular development but did not determine systemic safety. Later dose-de-escalation investigations demonstrated that substantially lower doses can remain biologically active. The minimum dose providing reliable disease control while minimizing systemic exposure remains dependent on agent and phenotype.[12]

RAINBOW randomized 225 infants. At 24 weeks, survival without active ROP, unfavorable retinal structure, or switching to another treatment modality occurred in 80% of infants receiving ranibizumab 0.2 mg, 75% receiving 0.1 mg, and 66% undergoing laser treatment.[13]

The OR for success with ranibizumab 0.2 mg versus laser was 2.19, but the 95% CI ranged from 0.99 to 4.82 and the P value was .051. The numerical results favored ranibizumab, but the prespecified criterion for statistical superiority was narrowly missed.

The clinical course after ranibizumab illustrates why acute success and total treatment burden are different outcomes. Incomplete initial regression was more common following laser, while delayed reactivation was more frequent after ranibizumab.[14]

Approximately one quarter of infants in each treatment group required an additional procedure, although for different reasons and at different times. Planned two- and five-year extensions subsequently examined refraction, vision, and nonocular development.[14–16]

An intravitreal injection may be considerably shorter and less physiologically stressful than laser at the initial encounter. It may, however, require more frequent examinations and a longer interval during which missed follow-up can result in preventable progression.

FIREFLEYE randomized infants in a 2:1 ratio to aflibercept 0.4 mg or laser. Treatment success at 24 weeks was 85.5% with aflibercept and 82.1% with laser.[17]

Although the absolute results were favorable in both groups, the prespecified statistical criterion for noninferiority was not met. Similar numerical percentages cannot therefore be translated into a formal conclusion of noninferiority.

The trial provided a prospective population for two- and three-year follow-up and demonstrated that aflibercept can rapidly control severe acute ROP.[17–19]

Treatment selection among anti-VEGF agents should not be based exclusively on class-wide pooled results. Bevacizumab is a full-length antibody with prolonged systemic exposure and remains off-label for ROP in many settings.

Ranibizumab is an antibody fragment with shorter systemic persistence and randomized dose-specific evidence. Aflibercept is a VEGF-trap fusion protein with high binding affinity and randomized phase 3 data.

Differences in reactivation may reflect pharmacological half-life, administered dose, retinal zone, retreatment criteria, and follow-up schedules as much as intrinsic efficacy. Adequately powered direct comparisons using standardized dosing remain limited.

5.3 REACTIVATION AND PERSISTENT AVASCULAR RETINA

After anti-VEGF treatment, plus disease and neovascular activity may regress rapidly while peripheral vascularization remains incomplete. The subsequent course may consist of

progressive physiological vascularization, persistent avascular retina without activity, or disease reactivation at the previous vascular–avascular junction.[1]

Reactivation can occur later than recurrence after conventional laser and has been reported beyond the age at which many infants would otherwise have completed acute ROP screening. ICROP3 therefore distinguishes regression and reactivation patterns following pharmacological therapy.[1]

A systematic review focusing on recurrence and retreatment found considerable heterogeneity according to agent and zone. Ranibizumab was associated with more recurrence than laser in a subgroup analysis, and zone II disease demonstrated greater recurrence after anti-VEGF therapy. Pooled retreatment estimates were imprecise and heterogeneity was substantial.[20]

The appropriate conclusion is not that one modality invariably produces more recurrence. Reactivation following anti-VEGF therapy is less predictable and is influenced by the molecule, dose, retinal location, and treatment protocol.

Surveillance should continue until retinal vascularization is complete or until residual avascular retina has been evaluated and a deliberate management plan has been established.

Wide-field imaging and fluorescein angiography can document arrested vascularization, leakage, shunting, and recurrence when clinical examination is inconclusive. No universally accepted angiographic threshold exists for prophylactic laser of persistent avascular retina.

Supplemental laser may be appropriate for reactivation, persistent leakage or neovascular activity, or circumstances in which continued surveillance cannot be performed safely. Routine ablation of every residual avascular area following successful anti-VEGF therapy is not supported by a validated universal rule.

The family's ability to return for repeated examinations is therefore part of treatment selection rather than an administrative consideration. A modality with a favorable anatomical and refractive profile can become unsafe when follow-up is unreliable.

Caregivers should understand that rapid regression after injection is not equivalent to complete retinal vascularization and that missed appointments may have irreversible consequences.

5.4 REFRACTIVE DEVELOPMENT

The largest and most consistent long-term advantage of anti-VEGF therapy is the lower frequency of myopia, particularly very high myopia.

In the BEAT-ROP refractive follow-up at a mean age of 2.5 years, myopia of −8 diopters or worse occurred in 3.8% of zone I eyes treated with bevacizumab and 51.4% of those treated with laser. Among posterior zone II eyes, the corresponding proportions were 1.7% and 36.4%.[12]

Mean spherical equivalent differed by approximately 7 diopters in zone I. These differences are clinically important because high myopia increases spectacle dependence, anisometropic amblyopia, retinal risk, and the complexity of visual habilitation.

Laser-associated myopia cannot be explained exclusively by loss of peripheral retina. Premature eyes already demonstrate atypical anterior-segment development. Extensive laser may accentuate shallow anterior chambers, steep corneas, increased lens thickness, and altered anterior-segment growth.

Anti-VEGF treatment permits more physiological peripheral vascularization and ocular development but does not normalize the eye. Children treated with anti-VEGF agents may still develop myopia, astigmatism, anisometropia, strabismus, or amblyopia and require repeated cycloplegic refraction.

RAINBOW demonstrated persistence of the refractive difference after ranibizumab. At two years, myopia of −5 diopters or worse occurred in approximately 5% of eyes treated with ranibizumab 0.2 mg and 20% of laser-treated eyes.[15]

At five years, high myopia in at least one eye occurred in 8% of the 0.2-mg group, 15% of the 0.1-mg group, and 24% of the laser group.[16]

The gradient is consistent with greater retinal preservation but should not be interpreted as proof of a linear dose effect because the dose groups were not powered for that comparison.

FIREFLEYE next demonstrated a similar pattern after aflibercept. At two years, high myopia occurred in 7.8% of aflibercept-treated eyes and 21.7% of laser-treated eyes. Very high myopia occurred in 0.9% and 13.3%, respectively.[18]

At three years, high myopia remained less frequent after aflibercept, occurring in 8.9% compared with 24.1% after laser.[19]

The extension analyses were descriptive and included children who agreed to continued participation. Nevertheless, the agreement among bevacizumab, ranibizumab, and

aflibercept studies strengthens the conclusion that retinal ablation produces a greater myopic burden.

5.5 VISUAL ACUITY, OCULAR ALIGNMENT, AND CEREBRAL VISUAL FUNCTION

Anatomical success is necessary for vision but does not guarantee normal visual development.

At five years in RAINBOW, mean better-eye Early Treatment Diabetic Retinopathy Study letter scores were 66.8 after ranibizumab 0.2 mg, 64.6 after ranibizumab 0.1 mg, and 62.1 after laser.[16]

The adjusted difference between ranibizumab 0.2 mg and laser was 4.7 letters, with a 95% CI from −1.1 to 10.5. This interval is compatible with minimal difference or a clinically meaningful visual advantage.

Missing visual-acuity measurements and the difficulty of standardized testing in children with developmental impairment reduce the certainty of this comparison.

At three years in FIREFLEYE next, binocular best-corrected visual acuity was at least 20/40 in 66.7% of children originally treated with aflibercept and 47.8% of children treated with laser. Almost all participants achieved at least 20/200.[19]

These comparisons were descriptive, and visual-acuity testing at three years is less stable than school-age optotype assessment. They cannot establish superiority.

Similar fixation behavior can coexist with relevant differences in refraction, alignment, contrast sensitivity, visual fields, or functional vision.

Strabismus, nystagmus, amblyopia, optic atrophy, macular ectopia, and cerebral visual impairment are common among survivors of severe ROP and extreme prematurity. Treatment modality modifies only part of this risk.

Children require early cycloplegic refraction, ocular-alignment assessment, and amblyopia management. Evaluation should also consider visually guided reaching, crowding, visual attention, and orientation difficulties when visual acuity does not explain functional performance.

Long-term neurovisual care may require collaboration among pediatric ophthalmologists, retina specialists, neonatologists, developmental pediatricians, neurologists, orthoptists, low-vision professionals, and early-intervention services.

5.6 VITREORETINAL SURGERY

Progression to stage 4A, 4B, or 5 ROP changes the therapeutic objective from suppression of neovascular activity to relief of vitreoretinal traction and preservation or restoration of retinal attachment.

Lens-sparing vitrectomy, scleral buckling, or combined approaches may be used depending on the configuration of detachment and available surgical expertise.

Outcomes decline significantly after macular detachment and are particularly unfavorable in stage 5 disease. In the ETROP surgical experience, macular attachment was obtained in approximately one third of eyes with retinal detachment. Favorable visual acuity was concentrated among stage 4A eyes. No stage 5 eye achieved vision better than light perception in the initial report.[21]

Surgery can preserve useful form vision in selected stage 4 eyes, but anatomical reattachment does not eliminate macular distortion, photoreceptor injury, optic-nerve damage, amblyopia, or cerebral visual impairment.

The limited surgical window and strong dependence on disease stage reinforce the importance of timely primary treatment and urgent referral when tractional changes develop.

Families should be counseled that anatomical reattachment and functional vision represent distinct outcomes.

5.7 NEURODEVELOPMENTAL SAFETY

The neurodevelopmental safety question is biologically plausible because VEGF contributes to organ development and intravitreal anti-VEGF agents can reach the systemic circulation.

Causal interpretation cannot, however, be based on biological plausibility alone. Infants selected for injection are often smaller, more systemically unstable, affected by more posterior disease, or considered poor candidates for prolonged anesthesia.

The same characteristics independently predict mortality and neurodevelopmental impairment. Even extensive statistical adjustment cannot reconstruct unmeasured factors such as acute physiological instability, detailed cerebral imaging, clinician rationale for treatment, socioeconomic adversity, or severity within a diagnostic category.

A Canadian observational cohort reported a median Bayley Scales of Infant and Toddler Development, Third Edition motor score of 81 after bevacizumab and 88 after laser. The adjusted OR for severe neurodevelopmental disability was 3.1 after bevacizumab.[22]

This result appropriately generated concern. Only 27 infants received bevacizumab, however, and they had greater systemic illness and more severe ROP. Follow-up was also incomplete.

The finding is compatible with systemic toxicity, residual confounding, or a combination of both and cannot independently establish causality.

A larger Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network cohort included 405 extremely preterm infants. The primary composite of death or severe neurodevelopmental impairment did not differ significantly between bevacizumab and surgical treatment. Severe impairment alone was also not significantly different.[23]

Adjusted odds were higher after bevacizumab for mortality, a cognitive score below 85, and Gross Motor Function Classification System level 2 or higher. The bevacizumab group had lower birth weight and longer durations of mechanical ventilation and oxygen exposure, while disease zone was unavailable.[23]

These findings remain concerning but are highly vulnerable to treatment-selection bias.

Prospective extensions of anti-VEGF trials provide a complementary perspective. Two-year follow-up in CARE-ROP did not identify a dose-related developmental safety pattern, and five-year findings were broadly reassuring.[24,25]

Only 14 children completed ophthalmological assessment and five completed pediatric assessment at five years. The study was therefore incapable of excluding clinically important differences.

RAINBOW and FIREFLEYE next did not demonstrate patterns suggesting poorer nonocular development after ranibizumab or aflibercept. These studies benefited from randomized parent trials, prospective data collection, and defined treatment protocols.[16,18,19]

Their limitations include attrition, voluntary participation in extensions, heterogeneous developmental testing, and inadequate statistical power for rare events or small differences. They are reassuring but not definitive.

A meta-analysis published in 2023 found that ROP itself was associated with cognitive impairment, cerebral palsy, behavioral difficulties, and composite neurodevelopmental impairment. In adjusted comparisons, anti-VEGF treatment was associated with moderate cognitive impairment compared with laser, but the evidence was rated as very low certainty.[26]

This distinction is essential. Severe ROP is a marker of broad developmental vulnerability, whereas the incremental effect of a particular treatment remains uncertain.

A 2026 meta-analysis included 12 randomized trials and 58 observational studies. Anti-VEGF therapy was not associated with a pooled difference in developmental delay or cerebral palsy, with an RR of 1.05 and a 95% CI of 0.96–1.15.[27]

Overall mortality was higher after anti-VEGF therapy, but the association was confined to observational studies. The pooled mortality RR was 1.85 in observational studies and 1.02 in randomized trials.[27]

The difference according to study design strongly suggests confounding by indication and neonatal illness, although it does not exclude a small true treatment effect.

An American Academy of Ophthalmology assessment reviewed 26 comparative reports. Twenty studies, including all randomized trials, found no statistically significant treatment-group difference in neurodevelopment. Four favored laser, while two favored anti-VEGF therapy or identified poorer outcomes following photocoagulation.[28]

Only five studies assessed intelligence after four years of age, and none found a significant difference in intelligence quotient. No included investigation was specifically powered to identify a small neurodevelopmental effect.[28]

The most balanced conclusion is that current evidence does not support a large harmful effect, while smaller molecule-, dose-, or subgroup-specific effects remain unresolved.

Table 2

Comparative evidence concerning neurodevelopment after treatment of retinopathy of prematurity

Study	Design and sample	Developmental outcome	Quantitative finding	Principal limitation
Morin et al., 2016[22]	Observational cohort; 125 infants, including 27 treated with bevacizumab	Bayley-III and severe neurodevelopmental disability at 18 months	Median motor score 81 versus 88; adjusted OR for severe disability 3.1	Small exposed group, baseline illness imbalance, and residual confounding
Natarajan et al., 2019[23]	Neonatal Research Network cohort; 405 infants	Death or severe neurodevelopmental impairment at 18–26 months	Death or severe impairment adjusted OR 1.42; severe impairment adjusted OR 1.14; death adjusted OR 2.54	Nonrandomized treatment, greater respiratory burden after bevacizumab,

Study	Design and sample	Developmental outcome	Quantitative finding	Principal limitation
				and unavailable disease zone
CARE-ROP, 2022 and 2025[24,25]	Randomized ranibizumab dose pilot; 19 infants initially	Standardized pediatric follow-up	Two-year findings reassuring; five-year comparison impossible because only five pediatric assessments were completed	Profoundly underpowered and no laser comparator
RAINBOW extension, 2024[16]	Randomized parent trial; 156 children assessed at five years	Growth and nonocular development	No clinically meaningful treatment-group pattern	Not powered to exclude small developmental differences
FIREFLEYE next, 2024 and 2026[18,19]	Prospective extension; 100 enrolled and 90 with three-year data	Bayley-III, adaptive behavior, growth, and neurological safety	No relevant between-group developmental difference through two years; expected systemic outcomes at three years	Voluntary extension enrollment and descriptive analyses
Diggikar et al., 2023[26]	Systematic review and meta-analysis	Cognitive impairment, cerebral palsy, and behavioral outcomes	Any ROP: cognitive impairment OR 2.56 and cerebral palsy OR 2.26; anti-VEGF versus laser: adjusted OR 1.93 for moderate cognitive impairment	Treatment comparison had very low certainty
Wang et al., 2026[27]	Meta-analysis of 70 studies and 10,516 infants	Neurodevelopment and mortality	Neurodevelopment RR 1.05; mortality RR 1.68 overall, 1.85 in observational studies, and 1.02 in randomized trials	Divergence according to study design indicates probable confounding
AAO assessment, 2026[28]	Evidence assessment of 26 comparative studies	Neurodevelopment after anti-VEGF therapy or laser	Twenty of 26 studies found no significant difference; no study found a difference in intelligence after four years	No study was powered to establish developmental equivalence

AAO: American Academy of Ophthalmology; CI: confidence interval; OR: odds ratio; ROP: retinopathy of prematurity; RR: risk ratio.

5.8 INTEGRATING OCULAR BENEFITS AND SYSTEMIC UNCERTAINTY

The overall benefit gradient is clinically coherent. Anti-VEGF therapy preserves peripheral retina and is associated with less myopia, fewer retinal detachments, and fewer surgical interventions in pooled analyses.

These advantages are particularly relevant in posterior disease, in which laser treatment would be extensive and technically difficult.

Laser more definitively eliminates the angiogenic stimulus and may be preferred when prolonged surveillance cannot be guaranteed, when the disease is more anterior and readily treatable, or when systemic anti-VEGF exposure is a major concern.

The observational mortality association should neither be dismissed nor overstated. The pooled observational estimate was elevated, while the randomized estimate was neutral but imprecise.

Critically ill infants are more likely to receive a short bedside injection than prolonged laser treatment requiring sedation or anesthesia. Treatment selection can therefore generate a mortality association even if the drug has no causal effect.

Conversely, randomized trials are too small to exclude uncommon systemic harm. Shared decision-making should communicate both limitations.

Combination treatment is not a default compromise. Anti-VEGF treatment followed by laser may be appropriate for reactivation, persistent active avascular retina, incomplete response, or an anticipated loss to follow-up.

Routine immediate combination therapy sacrifices part of the retinal-preservation benefit and increases treatment exposure without a universally demonstrated long-term advantage. Sequential treatment should respond to the biological course of the individual eye.

Dose minimization is theoretically advantageous but must not compromise disease control. An insufficient dose requiring multiple injections or permitting progression to detachment may produce greater systemic and ocular burden than one effective initial treatment.

Dose-finding studies should evaluate cumulative exposure, retreatment, vascularization, reactivation, neurodevelopment, and functional vision rather than selecting doses according to short-term regression alone.

5.9 LONGITUDINAL NEUROVISUAL FOLLOW-UP

Treatment should begin with accurate ICROP3 classification, documentation of both eyes, and evaluation of systemic stability.

Type 1 ROP should be treated promptly. Selection between laser and anti-VEGF therapy should consider zone, extent, aggressive characteristics, media clarity, expected laser burden, anesthesia risk, drug availability, and the family's capacity for prolonged follow-up.

The anticipated surveillance pathway should be established before treatment whenever the clinical situation permits.

Following treatment, regression of plus disease, ridge activity, hemorrhage, and neovascularization should be serially documented.

After laser, examinations should identify untreated skip areas and persistent activity. Following anti-VEGF therapy, clinicians must document progression of peripheral vascularization, persistent avascular retina, and reactivation.

Transfers between hospitals or clinicians should include the drug, dose, laterality, treatment date, postmenstrual age, retinal zone and stage, response, and scheduled follow-up.

Neurovisual surveillance should continue after the acute ROP period. Cycloplegic refraction and ocular-alignment assessment are required during infancy and early childhood, with timely spectacle correction and amblyopia treatment.

Children with severe ROP, retinal detachment, neurological injury, developmental delay, nystagmus, impaired visual attention, or functional vision inconsistent with ocular findings require multidisciplinary evaluation for cerebral visual impairment and early visual habilitation.

Table 3

Modality-specific balance and follow-up requirements

Modality	Principal advantage	Distinct burden or risk	Follow-up emphasis	Clinical situation favoring use
Laser photocoagulation	Durable ablation, established effectiveness, and no systemic anti-VEGF exposure	High myopia, peripheral-field loss, procedural burden, and possible skip areas	Confirmation of complete treatment and regression followed by lifelong pediatric ophthalmic care	More anterior type 1 disease or inability to guarantee prolonged post-injection surveillance
Bevacizumab	Rapid control, retinal preservation, strong zone I efficacy, and substantially less very high myopia	Prolonged systemic exposure, late reactivation, and persistent avascular retina	Frequent examination until vascular maturation or a deliberate endpoint	Zone I or aggressive posterior disease when reliable follow-up is assured
Ranibizumab	Randomized dose data, shorter systemic persistence, and favorable refractive profile	Reactivation and repeat treatment may occur	Prolonged follow-up with particular attention to the reactivation period	Posterior disease when shorter systemic persistence is prioritized
Aflibercept	High acute effectiveness and prospective two- and three-year structural data	Original noninferiority criterion not satisfied and systemic safety still under investigation	Surveillance until a documented vascular endpoint	Severe ROP in settings with appropriate access and protocolized follow-up
Vitrectomy or scleral buckle	Potential reattachment and	Limited therapeutic window, unfavorable	Retinal, glaucoma, refractive, low-vision,	Tractional retinal detachment

Modality	Principal advantage	Distinct burden or risk	Follow-up emphasis	Clinical situation favoring use
	preservation of form vision in selected stage 4 eyes	stage 5 cataract, glaucoma, reoperation, and amblyopia	prognosis, and developmental surveillance	requiring urgent specialist treatment

The initial procedure lasts minutes or hours, while neurovisual development continues for years. The quality and continuity of follow-up are therefore part of the treatment itself.

6 LIMITATIONS

This article used a structured narrative method rather than a new systematic review with duplicate screening, prospective registration, and de novo meta-analysis. Publication bias and incomplete retrieval remain possible.

Definitions varied across studies. Treatment success could include survival, absence of active disease, absence of unfavorable retinal structure, and no change in treatment modality. Recurrence, reactivation, and retreatment were not uniformly defined, and refractive thresholds differed.

Developmental outcomes were measured using different Bayley editions, ages, thresholds, composite definitions, and approaches to mortality. These differences limit direct comparisons and make a single class-wide treatment effect potentially misleading.

Several ocular outcomes were analyzed at the eye level, while systemic and developmental outcomes occur at the infant level. Studies failing to account for correlation between two eyes may overestimate statistical precision.

Trial extensions may also lose some protection provided by initial randomization when participation and successful outcome measurement differ according to treatment group or developmental ability.

Confounding by indication is the principal limitation of neurodevelopmental evidence. Anti-VEGF therapy may be preferentially selected for smaller or more critically ill infants, posterior ROP, poor pupillary dilation, or increased anesthesia risk.

Adjustment for gestational age, birth weight, bronchopulmonary dysplasia, intraventricular hemorrhage, sepsis, necrotizing enterocolitis, ventilation, and socioeconomic characteristics reduces but cannot eliminate this bias.

Randomized trials are generally too small to investigate rare systemic outcomes and were primarily designed to assess ocular effectiveness rather than developmental equivalence.

Long-term evidence after five years remains limited. School-age reading, executive function, visuospatial performance, contrast sensitivity, visual fields, quality of life, and cerebral visual impairment are rarely evaluated with standardized methods.

Evidence also remains insufficient to define the optimal anti-VEGF molecule and minimum effective dose, determine when persistent avascular retina should be treated, and establish when individual children can safely leave intensive surveillance.

7 CONCLUSION

Timely treatment of type 1 ROP improves the probability of favorable retinal structure and useful vision. ETROP demonstrated that treatment benefit depends on selecting the appropriate phenotype: earlier intervention improves outcomes in type 1 disease, whereas many type 2 eyes regress without treatment. This principle remains the foundation for evaluating newer pharmacological approaches.

Anti-VEGF therapy provides rapid disease control while preserving peripheral retina and is particularly valuable for zone I, aggressive posterior, or technically difficult ROP. Across bevacizumab, ranibizumab, and aflibercept studies, the most consistent long-term advantage over laser is a substantially lower frequency of high and very high myopia. Pooled evidence also suggests fewer retinal detachments and vitreoretinal surgical procedures, although conclusions must respect trial-specific statistical criteria and agent-specific evidence.

The cost of retinal preservation is a longer surveillance obligation. Reactivation, retreatment, and persistent avascular retina can occur after apparent disease regression, and their timing varies according to agent, dose, and retinal zone. Anti-VEGF therapy should therefore be selected only when follow-up can continue until a documented vascular endpoint or a deliberate plan for residual avascular retina is established.

Available evidence does not demonstrate a consistent clinically important neurodevelopmental disadvantage of anti-VEGF therapy compared with laser. Observational signals, particularly those involving bevacizumab, are biologically relevant but strongly confounded by prematurity, systemic illness, disease zone, and treatment selection. Randomized extensions are reassuring but underpowered to exclude small or late effects.

The lowest dose with established effectiveness in the relevant protocol should be used, and unnecessary repeated exposure should be avoided.

Long-term care must extend beyond retinal attachment. Every child treated for ROP requires refractive, alignment, and amblyopia surveillance, age-appropriate evaluation of visual function, and developmental assessment when indicated. The best treatment is not the modality with the simplest acute endpoint, but the individualized strategy that provides durable retinal control, minimizes avoidable refractive and systemic burden, guarantees follow-up, and connects the child with neurovisual rehabilitation when required.

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