

Analysis of Cochrane Systematic Reviews about retinopathy of prematurity

Análise das Revisões Sistemáticas da Cochrane sobre retinopatia da prematuridade

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ABSTRACT

Background: Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder that affects extremely premature infants and is the leading cause of irreversible blindness in childhood. **Objective:** This study presents a review of Cochrane systematic reviews about ROP. **Methods:** We analyzed and summarized the results of all intervention, prevention and treatment, from Cochrane Systematic Reviews (SR) for ROP designed to the highest standard of rigor to show the current position and propose studies that are missing for decision making. **Results:** Eight SR were analyzed in this study, four in prophylaxis and four in treatment of ROP. The outcome 'Beneficial effect of oral beta-blockers on progression to stage 3 ROP but not to stage 2 ROP with plus disease or to stage 4 or 5 ROP was the only one that presented moderate evidence quality, all the others outcomes presented evidence quality floating from low to very low. **Conclusion:** There is a lack of studies showing the quality of evidence in the treatment and prevention of retinopathy of prematurity, particularly in long-term outcomes after treatment in order to assess the impact and quality of life of these patients.

Keywords: Retinopathy of prematurity; Therapeutics; Prophylaxis; Evidence-based practice; Evidence-based medicine

RESUMO

Introdução: A retinopatia da prematuridade (ROP) é um distúrbio vasoproliferativo da retina que afeta recém nascidos extremamente prematuros e é a principal causa de cegueira irreversível na infância. **Objetivo:** Este estudo apresenta uma revisão das revisões sistemáticas da Cochrane sobre ROP. **Métodos:** Analisamos e resumimos os resultados de todas as intervenções, prevenção e tratamento, das revisões sistemáticas (SR) da Cochrane para ROP, projetada com o mais alto padrão de rigor para mostrar a posição atual e propor estudos que estão faltando para a tomada de decisão. **Resultados:** Oito RS foram analisados neste estudo, quatro em profilaxia e quatro em tratamento de ROP. O efeito benéfico dos betabloqueadores orais na progressão para a ROP do estágio 3, mas não para a ROP da fase 2 com doença positiva ou para a ROP da fase 4 ou 5 foi o único que apresentou qualidade de evidência moderada, todos os outros resultados apresentaram qualidade de evidência flutuante de baixo a muito baixo. **Conclusão:** Faltam estudos demonstrando a qualidade das evidências no tratamento e prevenção da retinopatia da prematuridade, principalmente em desfechos em longo prazo após o tratamento, a fim de avaliar o impacto e a qualidade de vida desses pacientes.

Descritores: Retinopatia da prematuridade; Terapêutica; Profilaxia; Prática baseada em evidências; Medicina baseada em evidências

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INTRODUCTION

It is estimated that the incidence of Retinopathy of Prematurity (ROP) is around 33.9%⁽¹⁾ to 59%⁽²⁾ in premature and the severe form of the disease revolves around 0 to 44.9%⁽³⁾, depending on the population studied, gestation time, time of survival of the preterm infant. This incidence should increase with the increase in the number of high-risk pregnancies and the improvement of the resources to give survival to the premature that increase the chance to develop the ROP.

ROP is a retinal neovascular disorder that primarily affects premature newborn infants. There is a difference between countries regarding the ROP screening, but the International Classification recommend the examination of infants with birth weights less than or equal to 1250 grams or less than 31 weeks of gestation.⁽⁴⁾

The stages of the disease are classified by the location (zones 1 to 3), severity (stages 1 to 5) and presence or absence of venous dilatation and arteriolar tortuosity (plus disease).⁽⁵⁾ Also, infants can be classified as having pre-threshold disease (zone 1 disease of any stage or zone 2, stage 2 with plus disease or zone 2, stage 3) or threshold disease (five contiguous or eight cumulative clock hours of stage 3, in zone 1 or 2 with plus disease).⁽⁶⁾ This classification is very important and necessary to define the most appropriate treatment.

Laser photocoagulation became the primary ROP treatment modality in the 1990s and is reportedly effective in more than 90% of ROP cases.^(5,6) In the past decade, intravitreal injection of anti-vascular endothelial growth factor (VEGF) has become increasingly popular in ROP treatment because of perceived advantages over laser photocoagulation, including less stress to the treated infant, more rapid improvement of tunica vasculosa lentis and plus disease, reduced future myopia, and possibly better peripheral vision.⁽⁷⁾ However, evidence to guide clinicians on the time course of recurrence, risk factors for ROP recurrence, and overall prognosis after treatment for ROP is scarce.

Thus, the aim of this study was to evaluate the evidence from Cochrane Systematic Reviews regarding the effectiveness and safety of prevention and treatments of ROP, the highest level of evidence made by the most appropriate methodology.

METHODS

This is a review of Cochrane Systematic Reviews in Retinopathy of Prematurity, designed and executed according to the highest standard of rigor to determine the current position for decision making. It was conducted in the Ophthalmology Service of Federal University of São Paulo (UNIFESP), Brazil.

We only included the last version of completed Cochrane Systematic Reviews that evaluated all the parameters in prevention and treatment of ROP. There was no restriction to the date of publication. The protocols of SR in progress, empty SR and withdrawn SR were not considered.

It includes participants with ROP or risk to develop ROP and all types of prevention and treatment of ROP.

We carried out an electronic sensitive search strategy in the Cochrane Library (via Wiley) on March 27, 2020 as presented in table 1.

The researchers independently selected and evaluated all the titles and abstracts of records that had initially been retrieved on the basis of the inclusion criteria in order to confirm their

Table 1
Search strategy in the Cochrane Library

Search Strategy
#1 MeSH descriptor: [Retinopathy of prematurity] explode all trees
#2 (Prematurity Retinopathies) or (Fibroplasias, Retrolental) or (Prematurity Retinopathy) or (Retrolental Fibroplasias) or (Fibroplasia, Retrolental) or (Retrolental Fibroplasia)
#3 #1 or #2
Filters In Cochrane Reviews; in Title, Abstract and Keywords.

eligibility, in accordance with the inclusion criteria. The full texts of records with the potential for inclusion were read to confirm whether they should be included.

We presented all the included reviews in a qualitative synthesis considering the respective PICO (population, intervention, comparator and outcomes), SR methods, quality of evidence and its implications.

RESULTS

Search results

We found 62 systematic reviews (SR) with the strategy search, seven fulfilled the inclusion criterias⁽⁸⁻¹⁴⁾ and were included in this overview. Four SR^(8,10,11,12) approach to prophylaxis for ROP and four SR^(8,9,13,14) approach the treatment for ROP as summarized in table 2 and a brief narrative synthesis of each SR is presented below. The quality of evidence of the outcomes assessed by GRADE⁽¹⁵⁾ whenever it is presented by the review author both in table as in narrative synthesis.

Prevention of Retinopathy of Prematurity

Beta-blockers⁽⁸⁾

Different experimental models showed a decrease in β -adrenergic function that can result in a reduction or exacerbation of vascular changes. Thus beta-blockers can act to inhibit vascular proliferation in retinal vascular diseases.⁽¹⁶⁾

Three RCT (randomized clinical trials) (N = 366), two studies with high risk of bias, that used propranolol versus placebo or no treatment as prophylaxis in preterm infants without ROP, stage 1 ROP (zone I), or stage 2 ROP (zone II) without plus disease in preterm neonates of less than 37 weeks' gestational age.

- Beta-blockers for prevention of ROP showed relative risk (RR) 0.32, 95% CI (0.12 to 0.86) in rescue treatment with anti VEGF but for primary prophylaxis (no meta analysis) RR 0.25, 95% CI (0.05 to 1.10) and for secondary prophylaxis (two trials) RR 0.41, 95% CI 0.11 to 1.50 it was not showed statistically significant.

- For prevention with laser/cryo RR 0.54, 95% CI 0.32 to 0.89. For Primary prophylaxis in rescue treatment with laser or cryo (no meta analysis) RR 0.68, 95% CI [0.35 to 1.32] not significant but for secondary prophylaxis (two trials) RR 0.41, 95% CI 0.19 to 0.90 was significant.

- For progression to stage 2 ROP with plus disease RR 0.25, 95% [0.03-2.16] with low quality of evidence but was not statistically significant as well as stage 3 ROP RR 0.60, 95% [0.37-0.96] and for stage 4 or 5 ROP RR 0.11, 95% [0.01-1.96] with moderate quality for this outcomes.

Table 2
Summary of findings

Systematic review	Characteristics	Objective	Intervention	Findings	Quality of evidence (GRADE approach*) (Summary of findings)
Betablockers for prevention and treatment of retinopathy of prematurity in preterm infants ⁽⁸⁾	Neonates of less than 37 weeks' gestational age.	To determine the effect of beta-blockers used as prophylactic either as treatment in ROP.	Oral propranolol (2 mg/ml syrup) at a dose of 0.5 mg/kg 6 hourly to (1 mg/ml saline solution) at a dose of 0.5 mg/kg 6-hourly.	Beneficial effects on the risk of requiring anti-VEGF agents. Beneficial effects of oral beta-blockers on the risk of requiring laser therapy. Beneficial effect of oral beta-blockers on progression to stage 3 ROP but not to stage 2 ROP with plus disease or to stage 4 or 5 ROP. Meta-analysis did not indicate a significant effect on arterial hypotension, bradycardia, complications of prematurity or mortality. None of the trials reported visual impairment.	Low quality of evidence. Low quality of evidence. Moderate quality of evidence Low quality of evidence.
Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity ⁽⁹⁾	Anti-VEGF compared with conventional laser therapy or laser/cryotherapy in preterm infants with type 1 ROP.	To evaluate the efficacy and safety of anti-VEGF alone or associated with cryo/laser.	Monotherapy: using only intravitreal anti-VEGF; Combination therapy: anti-VEGF with cryo/laser therapy;	Bevacizumab/ranibizumab as monotherapy did not reduce the risk of complete or partial retinal detachment. The risk of recurrence of ROP requiring retreatment did not differ between groups. Infants who received intravitreal bevacizumab had a significantly lower risk of refractive errors (very high myopia) at 30 months of age. Pegaptanib with laser therapy reduce the risk of retinal detachment when compared to laser/cryotherapy alone. There was no difference in the risk of perioperative retinal haemorrhages between the two groups.	Very low quality of evidence. Very low quality of evidence. Low quality of evidence. Low quality of evidence.
D-Penicillamine for preventing retinopathy of prematurity in preterm infants ⁽¹⁰⁾	Incidence and progression of ROP.	To determine the effect of prophylactic of D-penicillamine on the incidence of acute ROP or severe ROP in preterm infants.	D-penicillamine intravenous compared with no treatment or placebo.	The meta-analysis showed no significant differences in the risk of any stage nor severe ROP or death in all participants as well as in the subgroup of infants under 1500 g birth weight. No side effects nor spasticity or developmental delay in one year found significant differences.	Not related.

Early light reduction for preventing retinopathy of prematurity in very low birth weight infants ⁽¹¹⁾	Reduced light exposure to premature infants within the first seven days.	To determine whether light exposure reduces the incidence or progression of RoP among very low birth weight infants.	The reduction of early light exposure, it was not related light parameters.	This study did not show benefit on reduction of light exposure in preterm infants of any weight in prevention RoP.	Not related.
Local anaesthetic eye drops for prevention of pain in preterm infants undergoing screening for retinopathy of prematurity ⁽¹²⁾	Premature Infant Pain Profile (PIPP) score of pain with topical anaesthetic eye drops.	To assess pain during eye exam by the PIPP scale with or without the use of anesthetic eye drops.	Amethocaine, proxymetacaine, tetracaine and oxybuprocaine.	There is a non-significant reduction in pain scores at one minute and a non-significant increase at five minutes after speculum insertion. The PIPP score > 12 PIPP > 4 in one minute resulted in a reduction of pain favorable to the use of the statistically significant anesthetic	Not related.
Supplemental oxygen for the treatment of prethreshold retinopathy of prematurity ⁽¹³⁾	Preterm or low birth weight infants with RoP.	To determine whether supplemental oxygen reduces the progression of RoP and improves visual outcome.	It does not describe the amount of oxygen.	A single trial has shown that complementary oxygen has a tendency to reduce the progression of RoP; in infants without RoP showed significantly fewer children who progressed to the RoP threshold. No significant effects were observed in blindness or severe visual function at three months. Long-term visual outcomes were not reported.	Not related.
Peripheral retinal ablation for threshold retinopathy of prematurity in preterm infants ⁽¹⁴⁾	Infants with threshold RoP.	Does peripheral retinal ablation, by any means, reduce the incidence of adverse ophthalmic outcome?	Was considered cryotherapy, laser diode, laser argon, xenon arc photocoagulation.	Two trials showed laser favorable to reduce the risk of early unfavorable retinal structure as well as in early childhood and in visual acuity in early childhood. In addition, visual fields in sighted eyes were slightly smaller in the treated group.	Not related.

* GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) Approach - Working Group grades of evidence. High Quality of Evidence: Further research is very unlikely to change confidence in the estimate of effect; Moderate Quality of Evidence: Further research is likely to have an important impact in the confidence estimate of effect and may change the estimate; Low Quality of Evidence: Further research is very likely to have an important impact in the confidence estimate of effect and is likely to change the estimate; Very Low Quality of Evidence: Uncertain about the estimate. ⁽¹⁵⁾

- Nystagmus at six to 12 months' corrected age: RR 1.64, 95% [0.41-6.51] was not statistically significant.

- Refractive error at six to 12 months' corrected age RR 0.69, 95% [0.28-1.67] was not statistically significant.

Meta-analysis did not indicate complications of prematurity or mortality nor effects of beta-blockers as arterial hypotension or bradycardia, however, propranolol dosage in one study was reduced due to severe hypotension, bradycardia, and apnea in several participants. None of the trials reported on long-term visual impairment.

D-penicillamine ⁽¹⁰⁾

D-penicillamine is a powerful antioxidant and vasomodulator that could act in vascular proliferation⁽¹⁷⁾.

In the meta-analysis, three RCT were found for infants under 1500g birth weight, but with no significant difference. The grade of evidence was not related and both results were not statistically significant.

- Developing any ROP in the D-penicillamine group: RR 0.32, 95% CI (0.03 to 3.70)

- Severe ROP: 0.69, 95% CI (0.11 to 4.22).

Early light reduction ⁽¹¹⁾

In the past it was believed that the use of supplemental oxygen, excessive exposure to light and hypoxia were considered to be causes of ROP. Currently, it is known that ROP is a disease that presented vascular growth in premature infants due to relative hyperoxia in phase 1 (22 to 30 weeks postmenstrual age) and a decrease in levels of vascular endothelial growth factor (VEGF) increase in VEGF concentrations to compensate for the hypoxic retina in phase 2 (31 to 44 weeks postmenstrual age).^(18,19) Anyway we always look for prophylactic factors.

Four RCT (N=897) with reasonable methodological quality failed to show any reduction of early environmental light exposure among very low birth weight infants.

- Acute ROP infants < 2001 g birth weight showed RR 1.00, 95% CI (0.89, 1.13);

- Acute ROP infants < 1000 g birth weight showed RR 0.96, 95% CI (0.82, 1.13);

- Acute ROP infants 1000 to 2000 g birth weight showed RR 1.00, 95% CI (0.68, 1.49);

- Poor ROP all infants < 2001 g birth weight showed RR 1.13, 95% CI (0.49 to 2.61);

- Poor ROP all infants < 1000 g birth weight showed RR 10.24, 95% CI (0.51 to 203.83).

None of the outcomes were statistically significant nor significantly favorable to the intervention. The author concluded that bright light is not the cause of retinopathy of prematurity and that the reduction of exposure of the retina of premature infants to light has no effect on the incidence of the disease. However, the results were not statistically significant and the study did not present the summary of findings not allowing to evaluate the degree of evidence of the outcomes for the decision making.

There was no report on the secondary outcomes considered in this review: quality of life measures; and time of exposure to oxygen and the author does not describe the intensity or type of light assessed in this study.

Anaesthetic eye drops for prevention of pain during ophthalmological exam ⁽¹²⁾

Topical anesthesia is a medication with little or no side effects that can prevent pain on the eye exam when positioning the eyelid speculum or at the time of scleral indentation because neonates and infants are at increased risk of experiencing moderate to severe pain during hospital care.^(20,21)

Two RCT (N=124) evaluated pain using a PIPP (Premature Infant Pain Profile)⁽²²⁾ scale in infants undergoing ROP screening.

- Non significant reduction in pain scores at one minute and a nonsignificant increase at five minutes. PIPP score > 12 in one minute resulted in a statistically significant reduction in the number of patients experiencing typical pain RR 0.56, 95% CI [0.36 to 0.89].

- When pain was defined as an increase in PIPP > 4, there was a statistically significant reduction in the number of patients experiencing pain in one minute RR 0.70, 95% CI [0.52 to 0.94].

The author concluded that the topical proparacaine 30 seconds prior to the ophthalmological evaluation was associated with a reduction in pain scores especially at the time of speculum insertion.

PIPP score interpretation⁽²²⁾:

Scores of 0-6: generally indicate the infant has minimal or no pain.

Scores of 7-12: generally indicate slight to moderate pain.

Scores > 12: may indicate severe pain.

Treatment of Retinopathy of Prematurity

Beta-blockers ⁽⁸⁾

Presented above as a prophylactic among the outcomes, the therapeutic part was analyzed.

- For progression to stage 2 ROP with plus disease RR 0.25, 95% [0.03-2.16] with low quality of evidence but was not statistically significant as well as stage 3 ROP RR 0.60, 95% [0.37-0.96] and for stage 4 or 5 ROP RR 0.11, 95% [0.01-1.96] with moderate quality for this outcomes.

Anti VEGF ⁽⁹⁾

More recently, because vascular endothelial growth factor (VEGF) is a key factor in the progression of ROP, anti-VEGF agents have been used as a treatment modality. Currently, three anti-VEGF agents have been studied: Aflibercept (Eylea; Regeneron Pharmaceuticals, Inc, Tarrytown, NY), Bevacizumab (Avastin; Genentech, South San Francisco, Calif., USA) and Ranibizumab (Lucentis; Genentech, San Francisco, Calif., USA).^(23,24)

Six RCT (N= 383) infants with type 1 ROP. Five RCT compared intravitreal bevacizumab (n = 4) or ranibizumab (n = 1) with conventional laser therapy (monotherapy), while the sixth study compared intravitreal pegaptanib plus conventional laser therapy with laser/cryotherapy (combination therapy).

- Bevacizumab/ranibizumab did not reduce the risk of complete or partial retinal detachment (3 studies; N=272) RR 1.04, 95% CI 0.21 to 5.13; very low-quality evidence. Subgroup analysis showed a significant reduction in the risk of recurrence in infants with zone I ROP (RR 0.15, 95% CI 0.04 to 0.62), but an increased risk of recurrence in infants with zone II ROP was not significant (RR 2.53, 95% CI 1.01 to 6.32). Significant increase in the risk of recurrence of ROP in the eyes that received bevacizumab (RR 5.36, 95% CI 1.22 to 23.50), but it was not statistically significant.

Bevacizumab had a significantly lower risk of refractive errors (very high myopia) at 30 months of age (1 study; 211 eyes; RR 0.06, 95% CI 0.02 to 0.20; low-quality evidence).

- Association of laser / pegaptanib reduces the risk of retinal detachment when compared to laser/cryotherapy alone (152 eyes; RR 0.26, 95% CI 0.12 to 0.55; low-quality evidence). The incidence of recurrence of ROP by 55 weeks' postmenstrual age was also lower in the pegaptanib + laser therapy group (76 infants; RR 0.29, 95% CI 0.12 to 0.7; low-quality evidence)

- The risk of systemic adverse effects with any of the three anti-VEGF drugs is not known.

Supplemental oxygen⁽¹³⁾

The ROP stage 3 with plus disease has been associated with supplemental oxygen administration since 1940⁽²⁵⁾. The amount of oxygen babies receive in neonatal intensive care is very carefully monitored to try to lower the risk of ROP and limit the possibility of lung damage. One option is increasing the oxygen level to babies who are showing signs of worsening ROP. However, increased oxygen supplementation for babies with signs of worsening retinopathy of prematurity (ROP) may not prevent development of this eye disease, and may also lead to lung complications.

One trial included in this review (N= 649). Supplemental oxygen to reduce the progression to threshold ROP did not present statistical significance RR 0.84, 95% CI 0.70, 1.02. No significant effects were detected on blindness or severe visual function at three months corrected age, mortality, pneumonia, chronic lung disease or weight gain. Adverse pulmonary events, longer hospital stay and supplemental oxygen occurred in the higher oxygen saturation group and longer term visual outcomes were not reported. The degree of evidence was not shown.

Peripheral retinal ablation⁽¹⁴⁾

The ablation of the ischemic part of the retina can be done through 2 techniques to preserve macular vision: the cryoablation and laser therapy.⁽²⁶⁾

It is the most commonly used treatment to ROP and that technique emits beams of light over the pigmented epithelium cells of the retina, increasing the local temperature and causing coagulation and formation of the scar tissue by this abrasion, which helps to reduce the formation of blood vessels anomalous retina.⁽²⁷⁾

Two RCT showed that peripheral ablation reduces the risk of:

- early unfavorable retinal structure from RR 0.59 05% 0.47 to 0.74. (favorable to intervention with statistical significance)

- retinal structure in early childhood (5.5 yr) RR 0.81 95% CI 0.70 to 0.95. (favorable to intervention with statistical significance)

- unfavorable to visual acuity in early childhood RR -8.2 95% CI -12.31 to -4.14 (favorable to control). The degree of evidence was not shown.

DISCUSSION

In search of the best therapeutic and prophylactic evidence in ROP it was performed this review of Cochrane systematic reviews. It was searched for reviews that would show the long-term vision, the field of view, the anatomical changes of the children undergoing at each treatment and we observed the absence of these outcomes.

On prevention the use of oral beta-blockers may reduce the risk of progression to ROP stage 3 (but not to stage 4 or 5 ROP) and reduce the risk of need for laser or anti-VEGF treatment, but RS found evidence of low to moderate quality of evidence, it means that future studies can change decision making. The clinical relevance of these findings is uncertain, as it did not show long term vision results. Serious adverse events attributed to propranolol cause concern as there is insufficient evidence to determine the efficacy and safety of oral beta-blockers for the prevention of ROP because of the high risk of bias in two of the three included trials and the lack of functional outcomes of long term. The author concludes not recommending the routine use of oral propranolol for prevention of ROP in preterm infants requiring more adequately designed studies for decision making.

In the use of D – penicillamine, although RS has not found advantages in the prophylactic administration in preterm infants because it does not prevent acute or severe ROP, death or delay of neurodevelopment, it shows biological evidence⁽²⁸⁻³⁰⁾ that justifies insinuation in properly designed clinical trials to guide future decision making. The same way the RS of early environmental light exposure failed to show that bright light is not the cause of retinopathy of prematurity and that the reduction of exposure of the retina of premature infants to light has no effect on the incidence of the disease. In RS about topical anesthesia while the administration of topical anesthesia showed an improvement in pain scores compared with placebo, but screening remains a painful procedure and the author concluded that multi-modal approach to eliminating pain is required. Also, future research needs to be directed towards the question of whether infants without plus disease are more likely to respond to supplemental oxygen therapy than those with plus disease.

Related to treatment, the SR about anti-VEGF, although satisfactory for some outcomes and not for others, the quality of evidence was very low to low for most due to the risk of detection bias and other biases. According to GRADE-Quality of evidence, low means that future research is very likely to have an important impact and could change the evidence and very low means that persist the uncertainty. The effects on other critical outcomes and, more importantly, on the long-term systemic adverse effects of drugs are not known. Insufficient data prevent strong conclusions that favor the routine use of intravitreal anti-VEGF agents - as monotherapy or in conjunction with laser therapy - in preterm infants with type 1 ROP.

Finally, there is a lack of studies with well-defined protocols to guide which patients would be most suitable for anti-VEGF therapy and in which situation the laser would be better used. And also, if the best approach would be the combination of drugs or monotherapy, what are the chances of recurrence in each type of treatment, long-term ocular and systemic side effects and what is the most appropriate follow-up time. In addition, more investigation into the most efficient drugs, optimal dose of the anti-VEGF medication for ROP is needed. Thus, further prospective studies with larger study populations are required to compare treatment options for ROP treatment.

CONCLUSION

This review found seven Cochrane systematic reviews that evaluated interventions for prevention or treatment of ROP. Whether due to the quality of evidence ranging from moderate to very low, either because of the lack of statistical significance of

the meta-analyzes or because of the high risk of bias that some clinical trials present. All RS are unison in requesting studies with adequate designs addressing long-term outcomes term as visual acuity and in the short term requesting a confirmed assessment at the time of the examination and for adverse effects.

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