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Review article

Comparison of different agents and doses of anti-vascular endothelial growth factors (aflibercept, bevacizumab, conbercept, ranibizumab) versus laser for retinopathy of prematurity: A network meta-analysis

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ABSTRACT

Laser photocoagulation (LPC) and/or intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections constitute the current standard treatment for retinopathy of prematurity (ROP). This network meta-analysis focus on whether a ranking of interventions may be established for different dose levels of intravitreal injection of anti-VEGF agents (aflibercept, bevacizumab, conbercept, ranibizumab) as primary treatments for ROP versus laser in terms of retreatment rate as primary outcome, and time to retreatment and refractive error as secondary endpoints, since best anti-VEGF dosage remains under debate. Sixty-eight studies (15 randomized control trials and 53 nonrandomized studies) of 12,356 eyes of 6445 infants were retrieved from databases (2005 Jan. – 2023 June). Studies were evaluated for model fit, risk of bias and confidence of evidence in Network Meta-Analysis (CINeMA). Bayesian NMA showed that anti-VEGF drugs were not inferior to laser in terms of retreatment rate. For intravitreal bevacizumab (IVB), doses half of the conventional infant dose showed a low risk of retreatment rate (risk ratio (RR) of 1.43; 95% credible interval (CrI): 0.508, 4.03). On probability ranking as surface under the cumulative ranking curve (SUCRA) plot, half dose of bevacizumab had a better position than conventional and augmented (1.2–2 times the regular dose) doses. A similar probability trend was observed for half vs. conventional doses of aflibercept and ranibizumab. Conventional infant dose of conbercept showed the lowest risk for retreatment (RR 0.846; 95% CrI: 0.245, 2.91). For secondary endpoints, lower doses of anti-VEGF agents were associated with shorter times to retreatment. The largest changes were noted for the augmented doses of bevacizumab and ranibizumab (0.3 mg) with means of 14.1 weeks (95% CrI: 6.65, 21.6) and 12.8 weeks (95% CrI: 3.19, 20.9), respectively. Finally, NMA demonstrated better refractive profile for anti-VEGF than laser therapy, especially for the conventional infant doses of bevacizumab and ranibizumab which exhibited a significantly better refractive profile than LPC, with mean differences of 1.67 (spherical equivalent - diopters) (95% CrI: 0.705, 2.67) and 2.19 (95% CrI: 0.782, 3.59), respectively. In the SUCRA plots, LPC had a markedly different position with a higher probability for myopia. Further clinical trials comparing different intravitreal doses of anti-VEGF agents are needed, but our findings suggest that low doses of these drugs retain efficacy and may reduce ocular and systemic undesired events.

1. Introduction

Retinopathy of prematurity (ROP) is a serious neovascular disorder caused by proliferation of abnormal fibrovascular tissue in premature infants.[25] ROP is considered a biphasic disease with an initial oxygen-induced suppression of retinal blood vessel growth, followed by hypoxia-induced vascular endothelial growth factor (VEGF) formation and pathologic neovascularization.[37,114] Laser photocoagulation (LPC)

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is an established primary treatment for ROP and likely works by destroying the hypoxic VEGF-producing peripheral retina.[3,30] Intravitreal anti-VEGF therapy has been demonstrated beneficial while avoiding some disadvantages of laser.[104,116] The clinically available anti-VEGF agents differ in their potencies and binding to members of the VEGF family as well as in their intraocular half-lives, and the same drug may be used at different intravitreal dose levels. They also result in different systemic exposure levels with potential impact on the organogenesis[1,33] Compared to LPC, anti-VEGFs have less influence on eye growth and myopia development but appear to be associated with insufficient retinal vascularization, also called chronic vascular arrest, with subsequent ROP recurrence and need of retreatment.[4] The number of high-quality studies involving direct pairwise comparisons between anti-VEGFs is limited, thus increasing the difficulty of clinical decisions.[7,25]

To address these concerns, we conducted a network meta-analysis (NMA)[16] to compare intravitreal injection of anti-VEGF agents (aflibercept, bevacizumab, conbercept, ranibizumab) and laser therapy as primary treatments for ROP in terms of retreatment rate as main outcome, along with time to retreatment and refractive error (spherical equivalent) as secondary endpoints. Since there is a trend to reduce intravitreal doses of anti-VEGFs for minimizing toxicity, we focus on ranking results for different dose levels whenever available. The anti-VEFG drugs included and the number of studies retrieved in this work is enlarged with respect to previously published meta-analyses on this topic[7,93,94,112,126] in order to generate a broader evidence base and to improve the intervention effect estimates for comparisons, alongside with providing new data on probability ranking metrics for hierarchy of treatments. These results may help to inform the arduous clinical decision in this sight-threating disorder in preterm infants.

2. Methods

This NMA was conducted in accordance with a pre-specified protocol registered with PROSPERO (Prospective Register of Systematic Reviews), with the identification number CRD42022353416 and conformed with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist and recommendations outlined in the Cochrane Handbook.

2.1. Eligibility criteria for inclusion

2.1.1. Types of studies

We reviewed randomized controlled trials (RCTs) as well as non-randomized intervention studies (NRIS) that included preterm infants with ROP who underwent intravitreal anti-VEGF monotherapy and/or LPC. We excluded narrative and systematic reviews, meta-analyses, single-arm studies, case reports, letters to the editor, editorials, and commentaries. No restrictions of follow-up duration, language, location or journal of publication were imposed.

2.1.2. Types of participants

(1) Preterm infants with ROP
(2) Diagnosis of ROP must be made with a clinical exam
(3) There should not be any evidence of other vitreoretinal conditions aside from ROP

2.1.3. Type of interventions and comparators

We divided the interventions into 12 groups. The groups concerning each of the anti-VEGF agents studied were set in accordance to the different dose (mg) levels used in the literature in order to find differences in the intervention effect estimates and establish the probabilities of some treatments performing better than others, i.e. a treatment ranking. Thus, the conventional infant doses of the four anti-VEGFs are well established in the literature. Those doses of aflibercept, bevacizumab and ranibizumab smaller than the conventional infant dose, with values round about half this regular dose, were grouped according to published studies.[26,92,103,105,114,124] In the case of further reduced doses of bevacizumab, the diverse dose levels referred in the literature has been grouped as low and very low doses.[27] Additional clusters of doses larger than the conventional dose are tagged as augmented doses for bevacizumab (1.2 and 2 times)[79,89,92] and for ranibizumab (1.2 times).[9] This strategy of clustering different dose levels was necessary to assure a sufficient number of connected pairwise comparisons for the network plot because of the low count of patient/eyes particularly for the less conventional doses, but this implies assuming that small dose variations intragroup do not have a significant impact on study endpoints. The intervention nodes comprise laser therapy (LPC) and the different intravitreal anti-VEGF dose ranges, as follows (anti-VEFG doses are expressed in mg):

- LPC
- Intravitreal aflibercept, half the conventional infant dose (IVA_h): 0.4
- Intravitreal aflibercept, conventional infant dose (IVA_ci): 1
- Intravitreal bevacizumab, very low dose (IVB_vl): 0.002, 0.004, 0.008, 0.016
- Intravitreal bevacizumab, low dose (IVB_l): 0.031, 0.063, 0.125, 0.16
- Intravitreal bevacizumab, half the conventional infant dose (IVB_h): 0.25, 0.32. 0.5
- Intravitreal bevacizumab, conventional infant dose (IVB_ci): 0.625
- Intravitreal bevacizumab, augmented dose (IVB_a): 0.75, 1.25
- Intravitreal conbercept, conventional infant dose (IVC_ci): 0.25
- Intravitreal ranibizumab, half the conventional infant dose or half the augmented dose (IVR_h): 0.1, 0.12, 0.15
- Intravitreal ranibizumab, conventional infant dose (IVR_ci): 0.2, 0.25
- Intravitreal ranibizumab, augmented dose (IVR_a): 0.3

The volume of diluted solution (mg/mL) for each study is detailed in Table 1 – Characteristics of included studies, when specified by authors. These treatments are considered within the ophthalmologists' resources for treatment of either ROP or other retinal pathologies. Comparators could be either of these anti-VEGF agents or LPC therapy.

2.1.4. Type of outcomes measures

Studies were included if they provide at least one of the primary or secondary outcome data, mentioned below.

Primary outcomes:

- Retreatment rate: number of eyes needing an additional therapy. Additional treatment may be used for incomplete regression or disease reactivation after regression.

Secondary outcomes:

- Time to retreatment: number of weeks between the first and second treatment.
- Refractive error (spherical equivalent): Measured refraction errors after ROP treatment at the end of the follow-up period. The spherical equivalent (SE) was determined by adding together the spherical value and half of the cylindrical value.

2.2. Study selection, data extraction, and analyses

2.2.1. Study selection and data extraction

Two independent reviewers (JLO and AOS) separately performed an abstract screening, followed by a full-text assessment as well as data extraction from eligible studies. The discrepancies were resolved by discussion and consensus with other two authors (EM and HB). EMBASE (2005 - June 2023), PubMed (2005 - June 2023), Cochrane Library

Table 1
Characteristics of Included Studies.

No	Study	Study design	Treatment Intravitreal Doses	Gender M/F	GA weeks Mean (SD)	Mean Birth Weight (g) Mean (SD)	Location and severity of ROP	PMA at 1st treat. (wks) Mean (SD)	No of patiens	No eyes	Outcomes			Follow up (mos) Mean (SD)	Adverse events / Complications
											Eyes retreated	Time to Retreatment (wks) Mean (SD)	Sph.eq. Mean (SD)		
1	Chan et al 2016[6]	Retr.	LPC	NR	25.69 (2.17)	786(270)	4 APROP, 4 Z2S3	39.54 (1.49)	5	10	2			20.2 (10.0)	None
			IVR_ci 0.25 mg/ 0.025 mL		24.21 (0.51)	593(95)	3 Z2S2,6 Z2S3,1 Z2S4	36.25 (1.96)	4	8	6			24.8(5.3)	Retinal detachment (1 eye), non–progressive peripheral lens opacity (1 eye)
2	Chen S et al 2015[8]	Retr.	IVB_ci 0.625 mg/ 0.025 mL	11/10	26.3 (1.9)	869(200)	1 Z1S3, 20 Z2S3	36.8(3.5)	21	41	1		-0.3 (4.11)	12.9(0.9)	Localized preretinal hemorrhage (3 eyes)
			IVR_ci 0.25 mg/ 0.025 mL	6/10	26.2 (2.0)	848(300)	4 Z1S3, 12 Z2S3	35.9(2.7)	16	31	0		0.1 (1.36)	12.6 (0.9)	Localized preretinal hemorrhage (4 eyes)
3	Chen Y et al 2022[9]	Retr.	IVR_ci 0.25 mg/ 0.025 mL	NR	31.9 (3.1)	1158 (351)	NR	34.6(1.6)	82	146	26			GA 50 wks	None
			IVR_a 0.3 mg/0.03 mL		31.1 (3.2)	1072 (328)		34.2(1.6)	59	108	4				None
4	Chen YC et al 2018[11]	Retr.	IVB_ci 0.625 mg/ 0.025 mL	9/11	27.6 (2.43)	911(175)	3 Z2S2, 33 Z2S3	37.2(3.3)	20	36	4		-0.65 (3.83)	36	None
			IVR_ci 0.25 mg/ 0.025 mL	6/7	26.5 (2.28)	856(306)	7 Z1S3, 17 Z2S3, 2 Z3S3	36.1(2.7)	13	26	0		-0.12 (1.12)		None
5	Chen YC et al 2020[10]	Retr.	LPC	4/8	25.5 (1.24)	815(151)	1 Z2S2, 21 Z2S3	37.1(3.1)	12	22			-3.49 (4.39)	96	NR
			IVB_ci 0.625 mg/ 0.025 mL	2/11	26.5 (1.51)	862(197)	25 Z2S3	38.9(3.6)	13	25			-0.16 (2)		NR
6	Cheng et al 2020[13]	Retr.	IVC_ci 0.25 mg/ 0.025 mL	85/66	31.0 (2.99)	1955 (298)	22 APROP, 2 Z1S1, 3 Z1S2 8 Z1S3, 59 Z2S2, 189 Z2S3	40.14 (3.96)	145	43		11.21(1.41)		16.38 (2.4)	None
			IVR_ci 0.25 mg/ 0.025 mL	276/ 204	30.8 (1.88)	2045 (293)	132 APROP, 10 Z1S1, 25 Z1S2, 53 Z1S3, 154 Z2S2, 542 Z2S3	39.17 (3.75)	480	272		8.19(0.84)			None
7	Chmielarz-Czarnocinska et al 2021[15]	Retr.	LPC	NR	26(2)	868(236)	22 APROP, 8 Z1S1, 6 Z1S2, 10 Z1S3, 11 Z2S1, 56	NR	176	226	46			NR	NR

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Table 1 (*continued*)

No	Study	Study design	Treatment Intravitreal Doses	Gender M/F	GA weeks Mean (SD)	Mean Birth Weight (g) Mean (SD)	Location and severity of ROP	PMA at 1st treat. (wks) Mean (SD)	No of patiens	No eyes	Outcomes			Follow up (mos) Mean (SD)	Adverse events / Complications
											Eyes retreated	Time to Retreatment (wks) Mean (SD)	Sph.eq. Mean (SD)		
							Z2S2, 99 Z2S3								
			IVR_ci 0.25 mg/ 0.025 mL							120	80				NR
8	Demir et al 2019[17]	Retr.	LPC	34/31	28.4 (2.5)	1159 (444)	8 Z1, 56 Z2	35.7(2.3)	65	64	21			11	Macular traction (1 pt, 2 eyes)
			IVB_ci 0.625 mg/ 0.025 mL				25 Z1, 11 Z2, 21 APROP			57	11				Retinal detachment (1 pt, 2 eyes)
9	Demir et al 2021[18]	Retr.	LPC	4/8	29(2.9)	1447 (578)	Z2	NR	31	24			2.1 (2.24)		NR
			IVB_ci 0.625 mg/ 0.025 mL	9/10	29.4 (2.9)	1327 (393)	APROP, Z1, Z2 small pupil			38			0.46 (1.93)		NR
10	Ekinci et al 2020[21]	Retr.	LPC	9/18	28.7 (3.0)	1281 (438)	27 Z2	37.6(2.5)	27	27	2		1.1 (2.3)	11(2.3)	None
			IVA_ci 1 mg/0.025 mL	10/14	27.3 (2.8)	1095 (442)	22 Z1, 2 Z2	34.2(2.4)		24	6		1.5 (2.41)	10.5(2.6)	None
11	Ekinci et al 2021[22]	Retr.	IVA_h 0.4 mg/0.01 mL	7/9	27.9 (2.7)	1078 (400)	26 Z1, 6 Z2	34.8(2.8)	37	32	7	17.50(2.94)		34.1(5.5)	Dragging in the macula after LPC, applied due to non-response to IVA (1 eye)
			IVA_ci 1 mg/0.025 mL	10/11	28.9 (2.7)	1236 (414)	14 Z1, 28 Z2	36.1(1.9)		42	8	16.91(5.53)		34.3(7.5)	NR
12	Erol et al 2015[23]	Retr.	IVB_ci 0.625 mg	5/7	27.1 (2.5)	925(110)	9 Z2	35.3(1.7)	20	21	2	14.70(0.01)		4.62 (0.84)	Subconjunctival hemorrhage
			IVR_ci 0.25 mg	4/4	26.2 (2.7)	853(120)	10 Z1, 5 Z2	34.4(1)		15	6	6.60(3.16)		4.7(1.1)	Subconjunctival hemorrhage
13	Fleck et al 2022[26]	RCT	LPC	37/37	26.8 (2.06)	831(204)	20 APROP, 38 Z1, 90 Z2	39.8(5.8)	74	138	34	3.44(2.97)		5.63	Retinal haemorrhage (7 pts), conjunctival haemorrhage (2 pts) conjunctivitis (3 pts), conjunctival hyperaemia (2 pts), corneal opacity (2 pts)
			IVR_h 0.1 mg	37/40	26.8 (2.05)	886(299)	20 APROP, 39 Z1, 93 Z2	40.4(5.4)	77	152	42	7.40(4.10)			Endophthalmitis (1 pt), vitreous haemorrhage (4 pts), retinal haemorrhage (10 pts), conjunctival haemorrhage (6 pts), conjunctivitis (6 pts)
			IVR_ci 0.2 mg	33/41	26.5 (2.1)	791(244)	20 APROP, 35 Z1, 93 Z2	38.9(5.0)	74	148	40	7.16(3.59)			Cataract (1 pt), retinal haemorrhage (6 pts), conjunctival haemorrhage (6 pts), conjunctivitis (1 pt)
14	Freedman et al 2022[27]	RCT	IVB_vl 0.002 to 0.016 mg	71/49	24.9 (1.7)	698(302)	52 Z1, 61 Z2	NR	120	92	28	4.38(2.80)	-1.24 (3.08)	12	Mild vitreous hemorrhage (1 pt, 2 eyes), posterior, superior-

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Table 1 (*continued*)

No	Study	Study design	Treatment Intravitreal Doses	Gender M/F	GA weeks Mean (SD)	Mean Birth Weight (g) Mean (SD)	Location and severity of ROP	PMA at 1st treat. (wks) Mean (SD)	No of patiens	No eyes	Outcomes			Follow up (mos) Mean (SD)	Adverse events / Complications
											Eyes retreated	Time to Retreatment (wks) Mean (SD)	Sph.eq. Mean (SD)		
															nasal cataract (1 pt), vein occlusion (1 eye)
			IVB_l 0.031 to 0.16 mg							84	22	6.71(3.92)	-1.05 (3.81)		
			IVB_h 0.25 to 0.5 mg							25	5	10.43(2.40)	-0.73 (3.53)		
			IVB_ci 0.625 mg							10	2	8.21(5.55)	-2.48 (5.3)		
15	Geloneck et al 2014[29]	RCT	LPC	50/83	24.4 (1.5)	670.4 (158)	34 Z1, 41 Z2	34.85 (1.8)	109	101			-6.39 (6.50)	30	NR
			IVB_ci 0.625 mg/ 0.025 mL	47/78	24.3 (1.25	656.6 (126)	33 Z1, 42 Z2	35.17 (1.8)		110			-1.02 (2.98)		NR
16	Gunay et al 2015[31]	Retr.	LPC	6/9	27.3 (1.82)	941(282)	18 Z1, 12 Z2	33.9(2.2)	40	30	2		-6.66 (4.96)	24	Retinal detachment (2 eyes)
			IVB_ci 0.625 mg/ 0.025 mL	11/14	26.4 (1.82)	901(304)	25 Z1, 23 Z2	33.9(1.8)		48	3		0.42 (3.42)		NR
17	Gunay et al 2017[32]	Retr.	LPC	32/25	28.2 (2.5)	1195 (337)	7 Z1, 50 Z2	36.0(1.4)	134	113	2		-0.81 (4.94)	20.7(6.9)	None
			IVB_ci 0.625 mg/ 0.025 mL	21/34	27.3 (2.2)	1005 (411)	21 Z1, 34 Z2	34.2(1.9)		107	6	14.00(2.65)	-0.57 (4.54)	19.4(6.4)	Subconjunctival haemorrhage
			IVR_ci 0.25 mg/ 0.025 mL	13/9	28.0 (2.9)	1196 (467)	14 Z1, 8 Z2	35.6(1.6)		44	6	8.75(1.50)	0.78 (2.8)	19.0(4.8)	Subconjunctival haemorrhage
18	Han et al 2018[35]	NRIS	IVB_h 0.25 mg/ 0.01 mL	6/2	25.9 (1.2)	800(139)	6 Z1, 10 Z2	37.2(3.2)	8	8	0			11	Vitreous haemorrhage (1 pt)
			IVB_ci 0.625 mg/ 0.025 mL							8	0				NR
19	Harder et al 2013[36]	Retr.	LPC	7/6	25.2 (1.6)	622(153)	NR	NR	13	26	1		-4.41 (5.5)	12	Retinal detachment (1 eye)
			IVB_ci 0.625 mg/ 0.025 mL	7/5	25.3 (1.8)	717(197)			12	23	0		-1.04 (4.24)		
20	Huang et al 2018[40]	NRIS	IVA_ci 1 mg/0.025 mL	2/3	26.6 (2.95)	834(263)	1 Z1, 4 Z2	38.9 (3.13)	5	9	0			11(6.7)	None
			IVB_ci 0.625 mg/ 0.025 mL	4/5	25.7) 2.21)	725(187)		36.3(2.5)	9	17	0				None
21	Hwang et al 2015[41]	Retr.	LPC	13/4	24.8 (1.2)	701(118)	5 Z1, 27 Z2	36.1(2.1)	7	32	1	2.60	-5.3 (5.4)	34.5 (20.4)	Signs of increased IOP (1 eye)

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Table 1 (*continued*)

No	Study	Study design	Treatment Intravitreal Doses	Gender M/F	GA weeks Mean (SD)	Mean Birth Weight (g) Mean (SD)	Location and severity of ROP	PMA at 1st treat. (wks) Mean (SD)	No of patiens	No eyes	Outcomes			Follow up (mos) Mean (SD)	Adverse events / Complications
											Eyes retreated	Time to Retreatment (wks) Mean (SD)	Sph.eq. Mean (SD)		
			IVB_ci 0.625 mg/ 0.025 mL	6/5	24.2(1)	668(127)	16 Z1, 6 Z2	35.1(2.5)	11	22	3	9.00(5.70)	-2.4 (3.5)	21.7(8.8)	Preretinal or vitreous hemorrhage (4 eyes)
22	Isaac et al 2015[42]	Retr.	LPC	6/6	25.0 (1.1)	674(175)	8 Z1, 14 Z2	36.7(2.6)	12	22	1		-6.39 (4.41)	9	Increase in preexisting preretinal hemorrhage extending to the macular área (2 eyes)
			IVB_ci 0.625 mg/ 0.025 mL	10/3	25.2 (1.4)	722(131)	8 Z1, 15 Z2	37.6(1.7)	13	23	0		-3.57 (6.19)		None
23	Iwahashi et al 2021[43]	Retr.	IVB_h 0.25 mg/ 0.01 mL	15/22	24.7 (1.5)	629(216)	4 APROP, 26 S3, 7 S4A	33.7(3.3)	21	37	5	8.30(5.20)		39.0 (15.0)	None
			IVR_ci 0.25 mg/ 0.025 mL	25/18	25.0 (2.2)	714(291)	8 APROP, 29 S3, 6 S4A	36.9(2.6)	22	43	9	7.30(1.90)		10.6(6.6)	None
24	Jin et al 2018[46]	Retr.	IVC_ci 0.25 mg/ 0.025 mL	7/3	29.5 (1.37)	1369 (162)	2 APROP, 18 Z2	39.9(3.2)	10	20	3	4.15(0.01)		10	None
			IVR_ci 0.25 mg/ 0.025 mL	7/7	284 (1.62)	1171 (280)	6 APROP, 6 Z1, 16 Z2	42.3(5.2)	14	28	15	9.29(1.87)		12.3	None
25	Kabatas et al 2017[47]	Retr.	LPC	21/15	27.7 (2.7)	1112 (362)	22 APROP, 7 S3, 4 Z1, 32 Z2		36	72	10		-1.27 (2.8)	≥ 18	Preretinal hemorrhage (5 pts, 8 eyes), macular ectopia (1 pt, 2 eyes), exudative retinal detachment (1 pt, 2 eyes) Nystagmus (2 pts)
			IVB_ci 0.625 mg/ 0.025 mL	5/7	26.1 (2.3)	841(235)	10 APROP, 2S3, 2 Z1, 10 Z2		12	24	2		-1.49 (3.04)		Preretinal hemorrhage (2 pts, 3 eyes)
			IVR_ci 0.25 mg/ 0.025 mL	3/3	26 (1.26)	840(177)	5 APROP, 1 S3, 2 Z1, 4 Z2		6	12	2		-1.79 (2.87)		Preretinal hemorrhage (1 pt, 2 eyes)
26	Kang et al 2018[48]	Retr.	IVB_ci 0.625 mg/ 0.025 mL	32/20	26.9 (1.9)	941(296)	13 Z1, 78 Z2, 10 Z3	40.4(2.4)	52	101	8		0.1 (3.66)	30.9 (18.4)	Retinal detachment (1 eye), vitreous hemorrhage (1 eye), cataract (1 eye), pale disc (4 eyes), strabismus (21 eyes)
			IVR_ci 0.2 mg/0.02 mL	12/19	28.1 (3.2)	1257 (515)	21 Z1, 29 Z2, 2 Z3	39.2(2.3)	31	52	7		0.22(3)	13.9(2.3)	Vitreous hemorrhage (1 eye), macular dragging (1 eye), pale disc (4 eyes)
27	Kang et al 2019[49]	Retr.	LPC	44/41	28.8 (10.3)	1012 (301)	17 Z1, 120 Z2, 24 Z3	43.1 (15.3)	85	161	22	2.30(0.01)	-1.09 (3.68)	36.3 (31.9)	Retinal detachment (8 eyes), vitreous hemorrhage (1 eye), macular dragging (7 eyes), cataract (1 eye), pale disc (5 eyes), glaucoma (2 eyes), strabismus (26 eyes)

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Table 1 (*continued*)

No	Study	Study design	Treatment Intravitreal Doses	Gender M/F	GA weeks Mean (SD)	Mean Birth Weight (g) Mean (SD)	Location and severity of ROP	PMA at 1st treat. (wks) Mean (SD)	No of patiens	No eyes	Outcomes			Follow up (mos) Mean (SD)	Adverse events / Complications
											Eyes retreated	Time to Retreatment (wks) Mean (SD)	Sph.eq. Mean (SD)		
			IVR_ci 0.25 mg/ 0.025 mL	43/37	28.5 (2.5)	1049 (411)	34 Z1, 107 Z2, 12 Z3	40.0(2.5)	80	153	15	5.70(0.01)	0.11 (3.58)		Retinal detachment (1 eye), vitreous hemorrhage (2 eyes), macular dragging (1 eye), cataract (1 eye), pale disc (8 eyes), strabismus (21 eyes)
28	Karkhaneh et al 2016[50]	RCT	LPC	17/19	28.5 (2.0)	1202 (321)	4 Z2S2, 68 Z2S3	38.66 (4.1)	36	72	1			21	None
			IVB_ci 0.625 mg/ 0.025 mL	23/20	28.37 (2.0)	1133 (344)	3 Z2S2, 83 Z2S3	38.89 (3.9)	43	86	9				Subconjunctival haemorrhage
29	Kimyon et al 2018[51]	Retr.	IVB_ci 0.625 mg/ 0.025 mL	NR	29.3 (2.6)	1360 (372)	4 Z1S1, 14 Z1S2, 22 Z1S3	35.7(3.3)	37	40	4		-1.49 (2.38)	NR	Preretinal hemorrhages, vascular tortuosity (2 eyes)
			IVR_ci 0.25 mg/ 0.025 mL		30.1 (2.4)	1389 (406)	2 Z1S1, 11 Z1S2, 15 Z1S3	35.5(2.6)		28	2		0.98 (2.18)		Preretinal hemorrhages, choroid rupture temporal to the macula (1 eye)
30	Kong et al 2015[52]	NRIS	LPC	13/7	24.8 (1.8)	669(145)	1 Z1, 16 Z2, 2 Z3	37.4(3.9)	20	37	4		-5.61 (4.5)	NR	Unfavorable structural outcomes (4 eyes)
			IVB_ci 0.625 mg/ 0.025 mL	6/16	24.3 (1.3)	645(135)	3 Z1, 19 Z2	35.7(2.2)	22	43	3		-1.22 (2.95)		None
31	Kuo et al 2015[55]	Retr.	LPC	7/7	27.4 (2.9)	1007 (328)	14 S3	NR	14	14			-1.71 (1.27)	12	NR
			IVB_h 0.5 mg/0.02 mL	7/8	27.3 (2.9)	1080 (357)	15 S3		15	15			-1.53 (2.2)		NR
32	Lee et al 2018[57]	NRIS	LPC	8/5	26.6 (2.5)	803(145)	5 Z1, 19 Z2	NR	13	24	9		-2.5 (4.2)	NR	NR
			IVB_ci 0.625 mg/ 0.025 mL	8/9	26.6 (1.6)	874(229)	4 Z1, 29 Z2		17	33	14		-0.1 (3.3)		NR
33	Leng et al 2018[58]	Retr.	LPC	NR	31.4 (2.58)	1566 (229)	49 Z2 or Z3	NR	49	98	42			12.6	None
			IVR_ci 0.25 mg		28.8 (3.16)	1074 (204)	12 Z1 or APROP		12	24	10				None
34	Lepore et al 2018[60]	RCT	LPC	11/10	25.53	661.4	42 Z1S3	NR	21	21	1			48	Retinal detachment (1 eye)
			IVB_h 0.5 mg/0.02 mL							21	0				NR
35	Lepore et al 2020[59]	RCT	LPC	9/9	25.44	664.4	36 Z1S3	NR	18	18			-0.64 (4.55)	48	NR
			IVB_h 0.5 mg/0.02 mL							18			0.18 (3.04)		NR
36	Li et al 2015[62]	NRIS	LPC	NR	NR	NR	NR	NR	15	29			-3.48 (4.23)	NR	NR

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Table 1 (*continued*)

No	Study	Study design	Treatment Intravitreal Doses	Gender M/F	GA weeks Mean (SD)	Mean Birth Weight (g) Mean (SD)	Location and severity of ROP	PMA at 1st treat. (wks) Mean (SD)	No of patiens	No eyes	Outcomes			Follow up (mos) Mean (SD)	Adverse events / Complications
											Eyes retreated	Time to Retreatment (wks) Mean (SD)	Sph.eq. Mean (SD)		
			IVB_ci 0.625 mg/ 0.025 mL						21	41			-0.05 (3.01)		NR
37	Lin et al 2016[64]	Retr.	IVB_ci 0.625 mg/ 0.025 mL	5/3	26.5 (2.1)	938(200)	2 Z1, 11 Z2, 2 Z3	38.3(4.2)	8	15			-0.6 (3.86)	24	NR
			IVR_ci 0.25 mg/ 0.025 mL	4/9	26.2 (2.1)	811(287)	8 Z1, 17 Z2	35.2(2.0)	13	25			0.46 (1.36)		Preretinal hemorrhages (3 pts, 4 eyes)
38	Ling et al 2020[65]	Retr.	LPC	20/13	26.5 (2.2)	902(214)	7 Z1, 54 Z2	36.3(2.9)	33	61	11	3.60(1.40)		56.5 (25.2)	Retinal detachment (3 eyes)
			IVB_ci 0.625 mg/ 0.025 mL	67/51	26.4 (2.3)	852(243)	27 Z1, 204 Z2	36.2(2.6)	118	231	23	8.80(3.90)		46.3 (25.7)	NR
			IVR_ci 0.25 mg/ 0.025 mL	14/11	26.2 (1.6)	828(187)	5 Z1, 43 Z2	36.0(3.1)	25	48	10	8.30(1.60)		31.0 (12.6)	NR
39	Linghu et al 2022[66]	Retr.	LPC	118/ 102	29.8 (2.6)	1369 (343)	137 Z1 and APROP, 266 Z2	37.8 (2.94)	862	403	111			18.65 (15.4)	Retinal detachment (33 eyes)
			IVC_ci 0.25 mg/ 0.025 mL	330/ 312	22.8 (2.0)	1269 (370)	35 Z1 and APROP, 248 Z2	39.0 (11.47)		283	38			18.32 (11.5)	Retinal detachment (5 eyes)
			IVR_ci 0.25 mg/ 0.025 mL				220 Z1 and APROP, 696 Z2			916	268				Retinal detachment (27 eyes)
40	Lu et al 2022[68]	Retr.	LPC	8/6	27.6 (1.95)	1046 (259)	28 Z2S3	37.0 (1.72)	14	28			-2.43 (3.56)	60	NR
			IVR_ci 0.25 mg/ 0.025 mL	6/8	27.7 (1.81)	1047 (256)	27 Z2S3	36.4 (1.66)	14	27			-0.53 (3.12)	60	NR
41	Lyu et al 2019[69]	Retr.	LPC	0/5	28.8 (2.6)	1275 (360)	4 Z2S2, 6 Z2S3	42.6(3.4)	5	10	3			15.2(8.3)	None
			IVR_ci 0.25 mg/ 0.025 mL	7/9	29.0 (2.2)	1200 (360)	3 Z2S2, 14 Z2S3	40.8(1.0)	9	17	13			11.0(5.9)	Temporally dragged retina over the nerve (1 pt, 2 eyes)
42	Milani et al 2022[74]	Retr.	IVA_ci 1 mg/0.025 mL	21/19	28.9 (2.0)	1031 (212)	76 Z2	35.0(2.1)	40	76	12	15.50(0.98)	1.58 (1.3)	36	None
			IVB_ci 0.625 mg/ 0.025 mL	51/59	28.5 (2.1)	1060 (281)	210 Z2	34.9(2.2)	110	210	4	9.10(0.83)	1.78 (0.9)		None
43	Mintz_Hittner et al 2011[77]	RCT	LPC	50/83	24.4 (1.5)	670.4 (158)	34 Z1, 41 Z2	34.85 (1.8)	143	146	32	6.22(5.30)		13	Corneal opacity (1), lens opacity (3), macular dragging (16 eyes), retinal detachment (2 eyes)

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Table 1 (*continued*)

No	Study	Study design	Treatment Intravitreal Doses	Gender M/F	GA weeks Mean (SD)	Mean Birth Weight (g) Mean (SD)	Location and severity of ROP	PMA at 1st treat. (wks) Mean (SD)	No of patiens	No eyes	Outcomes			Follow up (mos) Mean (SD)	Adverse events / Complications
											Eyes retreated	Time to Retreatment (wks) Mean (SD)	Sph.eq. Mean (SD)		
			IVB_ci 0.625 mg/ 0.025 mL	47/78	24.3 (1.25)	656.6 (126)	33 Z1, 42 Z2	35.17 (1.8)		140	6	16.00(4.60)			Macular dragging (1 eye)
44	Moran et al 2014[79]	RCT	LPC	NR	35	NR	4 Z1S3, 10 Z2S3	35	14	14	1	2.00		24	NR
			IVB_a 1.25 mg/0.1 mL							14	3	16.00(1.00)			NR
45	Mori et al 2020[80]	Retr.	LPC	NR	24.7 (1.5)	626(180)	36 Z1, 74 Z2	35.5(2.7)	53	106	8			NR	NR
			IVB_ci 0.625 mg/ 0.025 mL						13	26	12				NR
46	Morrison et al 2018[82]	Retr.	LPC	275/ 219	25(2)	719(206)	7 Z1S1, 14 Z1S2, 92 Z1S3 92 Z2S2, 654 Z2S3, 2 Z3S3, 9 Z3S3	NR	494	970	7			4	Cataract (3 eyes), hyphema (15 eyes), glaucoma (1 eye), corneal ulcera or opacity (7 eyes)
			IVB_ci 0.625 mg/ 0.025 mL	11/7	25(1)	609(127)	1Z1S1, 1 Z1S2, 5 Z1S3, 2 Z2S2, 23 Z2S2		18	34	8				None
47	Mueller et al 2017[83]	Retr.	LPC	31/23	25.0 (0.42)	631(67.7)	4 Z1, 29 Z2 posterior, 21 Z2 peripheral	37.15 (0.62)	17	34	0		0.96 (0.69)	12-15	Exudative retinal detachment (1 pt, 2 eyes)
			IVB_ci 0.625 mg/ 0.025 mL						37	74	10		2.25 (2.04)		Corneal opacity (1 eye)
48	Murakami et al 2021[84]	Retr.	LPC		NR	25.7(1.4)	722(147)	10 Z2, 18 Z2	NR	14	28	0	-0.87 (3.14)	NR	Esotropia (3 pts)
			IVB_ci 0.625 mg/ 0.025 mL		26.8 (2.9)	816(369)	4 Z1, 20 Z2		12	24	4		-0.04 (0.31)		Retinal holes and retinal detachment (1 pt), intermittent exotropia (2 pts)
49	Nicoara et al 2016[87]	Retr.	LPC	5/1	29.8 (1.8)	1198 (236)	6 APROP	36.3(1.5)	6	12	2			19-33	NR
			IVB_ci 0.625 mg/ 0.025 mL	7/10	28.3 (1.5)	1095 (216)	17 APROP	34.4(1.6)	17	34	3				NR
50	OKeeffe et al 2016[89]	RCT	LPC	NR	25.8 (1.24)	795(188)	10 Z1, 5 Z2	34.4(1.6)	15	15	1		-2.73 (3.5)	NR	NR
			IVB_a 1.25 mg/0.1 mL							15	3		-0.9 (2.5)		NR

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Table 1 (*continued*)

No	Study	Study design	Treatment Intravitreal Doses	Gender M/F	GA weeks Mean (SD)	Mean Birth Weight (g) Mean (SD)	Location and severity of ROP	PMA at 1st treat. (wks) Mean (SD)	No of patiens	No eyes	Outcomes			Follow up (mos) Mean (SD)	Adverse events / Complications
											Eyes retreated	Time to Retreatment (wks) Mean (SD)	Sph.eq. Mean (SD)		
51	Patel et al 2023[92]	Retr.	IVB_l 0.031 to 0.16 mg	193/114	24.5	660	220 Z1, 323 Z2, 5 Z3	36	307	56	45			16.4	NR
			IVB_h 0.25 to 0.5 mg							37	12				NR
			IVB_ci 0.625 mg							309	95				NR
			IVB_a 0.75 mg to 1.25 mg							64	18				NR
			IVR_h 0.15 mg							62	32				NR
			IVR_ci 0.2 mg to 0.25 mg							33	24				NR
52	Riazi-esfahani et al 2021[96]	Retr.	IVA_ci 1 mg/0.025 mL	8/4	28.7 (2.3)	1205 (383)	10 Z1, 14 Z2	55(21)	12	24	14			5(1)	Subconjunctival hemorrhage
			IVB_ci 0.625 mg/ 0.025 mL	252/189	28.2(2)	1119 (311)	187 Z1, 678 Z2	59(19)	441	865	34			10(9)	Subconjunctival hemorrhage, vitreous hemorrhage (1 eye)
53	Roohipoor et al 2018[97]	Retr.	LPC	NR	< 34	< 2000	11 Z1, 251 Z2	NR	131	262	23		-2.84 (2.77)	NR	Macular dragging (6 eyes)
			IVB_ci 0.625 mg/ 0.025 mL				166 Z1, 558 Z2		362	724	106		-1.26 (3.19)		Macular dragging (4 eyes)
54	Roohipoor et al 2019[98]	RCT	LPC	NR	28.3 (2.1)	1273 (273)	6 Z2S2, 72 Z2S3	36.7(2.8)	39	78	2			21	NR
			IVB_ci 0.625 mg/ 0.025 mL		28.7 (1.9)	1232 (318)	12 Z2S2, 142 Z2S3	37.1(2.7)	77	154	5				Cataract (1 eye)
55	Sahin et al 2018[99]	NRIS	IVB_l 0.0625 mg/ 0.025 mL	22/23	27.8 (1.9)	1143 (332)	14 Z1, 31 Z2	35.18 (2.4)	45	90	0			NR	None
			IVB_ci 0.625 mg/ 0.025 mL	28/18	27.9 (2.5)	1105 (342)	15 Z1, 31 Z2	35.89 (2.5)	46	92	0				None
56	Stahl et al 2018[103]	RCT	IVR_h 0.12 mg/ 0.02 mL	6/4	25.7 (2.7)	624(230)	5 Z1, 15 Z2	37.1 (1.96)	10	18	4	12.43(2.97)		60	None
			IVR_ci 0.2 mg/0.02 mL	4/5	25.0 (1.7)	678(330)	3 Z1, 15 Z2	36.9 (1.87)	9	14	4	7.57(0.50)			New retinal haemorrhage (2 pts), increase in severity of plus disease (1 pt)
57	Stahl et al 2022[a102]	RCT	IVR_h 0.12 mg/ 0.02 mL	6/4	25.7 (2.7)	624(230)	5 Z1, 15 Z2	37.1 (1.96)	9	18			-1.9 (3.5)	24	Progression to stage 5 and blindness (1 pt, 2 eyes), motility

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Table 1 (*continued*)

No	Study	Study design	Treatment Intravitreal Doses	Gender M/F	GA weeks Mean (SD)	Mean Birth Weight (g) Mean (SD)	Location and severity of ROP	PMA at 1st treat. (wks) Mean (SD)	No of patiens	No eyes	Outcomes			Follow up (mos) Mean (SD)	Adverse events / Complications
											Eyes retreated	Time to Retreatment (wks) Mean (SD)	Sph.eq. Mean (SD)		
															restriction (1 pt), strabismus (4 pts), nystagmus (3 pts)
			IVR_ci 0.2 mg/0.02 mL	4/5	25.0 (1.7)	678(330)	3 Z1, 15 Z2	36.9 (1.87)	7	14			-0.75 (1.6)		Strabismus (3 pts), nystagmus (2 pts)
58	Stahl et al 2022b-FIREFLEYE[105]	RCT	LPC	19/19	26.0 (1.6)	811(73.2)	5 APROP, 7 Z1, 26 Z2	36.2 (2.3)	38	72	13	4.70(3.20)		NR	Retinal detachment (2 eyes), macular dragging (2 eyes)
			IVA_h 0.4 mg	41/34	26.4 (2.1)	828(94.8)	14 APROP, 15 Z1, 46 Z2	36.8(2.8)	75	146	33	8.62(4.05)			Retinal detachment (8 eyes), macular dragging (3 eyes), macular fold (1 eye), retrolental opacity (2 eyes)
59	Sukgen et al 2016[108]	Retr.	IVB_ci 0.625 mg/ 0.025 mL	13/9	28.68 (2.14)	1290 (298)	10 Z1, 12 Z2	34.5 (1.46)	22	44	4	9.42(1.20)		13	None
			IVR_ci 0.25 mg/ 0.025 mL	12/11	28.04 (2.34)	1148 (402)	11 Z1, 12 Z2	35.15 (1.66)	23	46	4	7.82(2.10)		13	None
60	Sukgen&Kocluk 2017[109]	Retr.	LPC	4/5	29.0 (2.6)	1288 (435)	1 Z1, 8 Z2	38.7 (2.46)	9	18	8			NR	None
			IVR_ci 0.25 mg/ 0.025 mL	5/2	28.4 (2.8)	1156 (3.72)		35.9(4.7)	7	13	9				None
61	Sukgen&Kocluk 2019[110]	Retr.	IVA_ci 1 mg/0.025 mL	18/18	28.3 (2.05)	1157 (298)	14 Z1, 22 Z2	34.7(1.4)	36	72	10	14.20(1.03)		19.6(4.5)	Peripheral subcapsular cataract (1 eye)
			IVR_ci 0.25 mg/ 0.025 mL	13/14	28.4 (2.58)	1127 (387)	11 Z1, 16 Z2	35.3(1.5)	27	54	26	8.20(0.92)		29.16 (6.06)	Cataract (1 pt, 2 eyes)
62	Suren et al 2022[111]	Retr.	IVA_ci 1 mg/0.025 mL	15/19	27 (2.11)	984(539)	10 Z1, 46 Z2	36(1.99)	34	56	8	12.00(2.47)	0.62 (1.35)	NR	None
			IVB_ci 0.625 mg/ 0.025 mL	17/13	27 (2.82)	1060 (539)	7 Z1, 47 Z2	36(2.26)	30	54	8	13.00(2.37)	-2.53 (2.58)		None
			IVR_ci 0.25 mg/ 0.025 mL	25/22	28(2.5)	1066 (313)	11 Z1, 66 Z2	36(2.12)	47	77	19	8.00(1.72)	0.28 (1.66)		None
63	Vujanovic et al 2017[117]	NRIS	LPC	23/22	30(4)	1200 (500)	NR	NR	45	90			-0.2 (5.19)	NR	NR
			IVB_ci 0.625 mg/ 0.025 mL	12/9	29(4)	1175 (425)			21	42			-0.5 (2.91)		NR
64	Wu et al 2021[121]	RCT	IVC_ci 0.25 mg/ 0.025 mL	16/14	28.27 (2.77)	1160 (480)	NR	35.26 (1.91)	30	60	10	8.71(6.62)		6	Cataract (2 eyes)

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Table 1 (*continued*)

No	Study	Study design	Treatment Intravitreal Doses	Gender M/F	GA weeks Mean (SD)	Mean Birth Weight (g) Mean (SD)	Location and severity of ROP	PMA at 1st treat. (wks) Mean (SD)	No of patiens	No eyes	Outcomes			Follow up (mos) Mean (SD)	Adverse events / Complications
											Eyes retreated	Time to Retreatment (wks) Mean (SD)	Sph.eq. Mean (SD)		
			IVR_ci 0.25 mg/ 0.025 mL	17/13	27.5 (2.7)	1089 (400)		36.08 (2.25)	30	60	14	8.29(2.56)			Cataract (1 eye)
65	Xu et al 2021[122]	Retr.	IVB_l 0.031 to 0.125 mg	67/48	24.48 (0.4)	626.2 (47.9)	158 Z1, 34 Z2	35.57 (0.57)	115	11	1			≥6	Retinal detachment (9 eyes), Mature cataract (1 pt)
			IVB_h 0.25 to 0.5 mg							110	9				
			IVB_ci 0.625 mg							50	6				
66	Zayek et al 2021[123]	Retr.	LPC	47/38	24 (1.48)	562.5 (128)	8 Z1, 73 Z2	35.4 (2.24)	85	170	4			18-24	NR
			IVB_ci 0.625 mg/ 0.025 mL	27/34	23 (1.48)	505.3 (127)	6 Z1, 55 Z2	34.0 (1.48)	61	122	20				NR
67	Zhang et al 2017[125]	RCT	LPC	14/11	28.27 (1.34)	1060 (240)	50 Z2	NR	25	50	2	1(0.01)		12.61 (2.89)	Vitreous and retinal hemorrhage (1 pt, 2 eyes)
			IVR_a 0.3 mg/0.03 mL	14/11	28.96 (1.59)	1220 (320)	50 Z2		25	50	26	12.62(7.93)		11.65 (3.4)	NR
68	Zhang et al 2022[124]	Retr.	IVB_l 0.125 mg	NR	25 (4.47)	603(26)	4 Z1 35 Z2	NR	20	16	10			14	None
			IVB_h 0.25 mg							16	6				
			IVR_h 0.15 mg							7	1				

APROP = Aggressive posterior Retinopathy of Prematurity; GA= gestational age; Gender M/F = Male/Female; IVA_ci = intravitreal aflibercept conventional infant dose; IVA_h = intravitreal aflibercept half dose; IVB_a = intravitreal bevacizumab augmented dose; IVB_ci = intravitreal bevacizumab conventional infant dose; IVB_h = intravitreal bevacizumab half dose; IVB_l = intravitreal bevacizumab low dose; IVB_vl = intravitreal bevacizumab very low dose; IVC_ci = intravitreal conbercept conventional infant dose; IVR_a = intravitreal ranibizumab augmented dose; IVR_ci = intravitreal ranibizumab conventional infant dose; IVR_h = intravitreal ranibizumab half dose; LPC = laser photocoagulation; Location and severity: Zone (Z1, Z2, Z3), Stage (S1, S2, S3, APROP); mos = months; NR = non registred; NRIS = non randomized interventional study; patient(s) = pt (s); PMA: Postmenstrual age. RCT = randomized clinical trial; Retr = retrospective; SD = standard deviation; Sph. Eq. = spherical equivalent; wks = weeks.

(June 2023) and gray literature databases were searched by using medical subject headings and free text to retrieve all the relevant records. Citation searching in included and excluded studies was also performed. The literature was organized using the reference management Mendeley Desktop software (version 1.19.8, ELSEVIER, UK). The data extracted from the recruited studies included: name of the first author, year of publication, study design, number of patients in each group, elective treatment (anti-VEGF agent and its dose or LPC), retreatment rate (number of eyes requiring retreatment for ROP), time to retreatment (number of weeks between initial and secondary treatment), as well as spherical equivalent at the end of the follow-up period. Demographic data were also collected, including gender, gestational age, mean birth weight, location and severity of ROP, postmenstrual age at first treatment, as well as treatment complications. Authors were contacted by e-mail correspondence to request missing data when needed. For studies involving the same patient populations, duplication of data was avoided by including only the most complete data set. The database search was completed June 30, 2023. Search strategy is indicated in the Section 6. and as Supplementary material 1.

2.2.2. Data synthesis and analysis

Data analysis was performed using the software MetaInsight V4.2.0.[90] The Meta-Insight tool utilizes the 'gemtc' and 'netmeta' packages of R for the Bayesian and frequentist framework, respectively. The estimates were synthesized with a Bayesian NMA for binary (retreatment rate) and continuous (time to retreatment and refractive error) outcomes measures. This model uses the Markov Chain Monte Carlo (MCMC) method to simulate from a probability distribution of interest.[24,34] Additionally, we performed a secondary analysis using the frequentist framework with the same software, and a league table and forest plot depicting the analysis results were obtained. All statistical analyses were executed using the random-effects model. This model was selected given the diversity among studies and the value of the Deviance Information Criterion (DIC).[19,101] Retreatment rate data were expressed as risk ratio (RR) and those of time to retreatment and spherical equivalent as mean + /- standard deviation along with 95% credible intervals (CrI) for each analysis. In those studies reporting results by using the median, we estimated the sample mean and standard deviation with the R package 'estmeansd'.[71] P-values < 0.05 were taken as statistically significant. Forest plots showing the summary effects of all anti-VEGF treatments in comparison with LPC, ranking tables, and radial surface under the cumulative ranking curve (SUCRA)[86] plots were also generated. We also performed a Welch's analysis of variance test and Games-Howell comparison test on the combined summary means to find which treatment pairs were statistically different for the secondary outcomes. Finally, a subgroup analysis exclusively including RCTs was performed. A meta-regression analysis was performed with Comprehensive Meta-analysis v3.0 software (Biostat) to assess whether clinical variables such as birth weight, gestational age and postmenstrual age at time of treatment were acting as effect modifiers across treatment comparisons.

2.2.3. Assessment of model fit

The model fit was evaluated by posterior mean of the residual deviance (Dbar), effective degrees of freedom (pD) and DIC estimates and visualized via the unrelated mean effect model (UME), the stem and leverage plots using the software MetaInsight V4.2.0.

2.2.4. Assessing risk of bias

The Cochrane risk-of-bias tool for randomized trials (RoB2)[107] was employed to assess the risk of bias in the eligible RCTs. The RoB2 tool has five domains of bias assessment pertinent to randomization process, deviation from the intended intervention, missing outcome data, outcome measurement, and selective reporting of the outcomes. Each study was reviewed and scored as high risk, low risk, or some concerns. For nonrandomized studies, we performed the risk of bias analysis using the Risk Of Bias in Non-randomized Studies of Interventions tool (ROBINS-I). This tool covers 6 fields: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.[106] Discrepancies between the reviewers were resolved through discussion until agreement. For visualizing risk-of-bias assessments we used the Risk-Of-Bias VISualization (robvis) package.[72]

2.2.5. Assessment of confidence

We evaluated the confidence of evidence generated across the trails using the Confidence in Network Meta-Analysis (CINeMA approach)[88] and performed in the CINeMA app[91]. CINeMA uses six domains to explore the confidence in the network result. All the domains (within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence) were rated as 'no concerns,' 'some concerns' or 'major concerns' apart from reporting bias, which was reported as 'suspected' or 'undetected.' Within study bias was estimated with the incorporation of the scores of the ROB2 and ROBINS-I judgements. To assess within-study and across-study bias and the small-study effects, the online ROB-MEN (Risk Of Bias due to Missing Evidence in Network meta-analysis) tool was used.[14] The final overall judgment on the confidence of evidence for each treatment comparison is rated 'very low,' 'low,' 'moderate' or 'high". For all outcomes, we assessed potential breaches in the transitivity assumption required for NMA, by checking the distribution of potential effect modifiers across studies grouped by treatment comparison. To check the consistency assumption, the inconsistency test with the 'nodesplit' model was undertaken using the software MetaInsight V4.2.0.

3. Results

3.1. Characteristics of included studies

The electronic databases search identified a total of 713 references, 344 articles from EMBASE, 81 articles from Cochrane, and 288 articles from Pubmed. After the removal of duplicated records, there were 448 articles. The titles and abstracts were screened for relevance to our research question. Afterwards, 93 papers remained, for which full text were retrieved and assessed for eligibility. We excluded 33 studies that did not meet the eligibility criteria and we added 8 studies identified from citation searching.

Therefore, 68 studies were included in the meta-analysis, in which 15 were RCTs [26,27,29,50,59,60,77,79,89,98,102,103,105,121,125] and 53 were NRIS [6,8–11,13,15,17,18,21–23,31,32,35,36,40–43,46–49,51,52,55,57,58,62,64–66,68,69,74,80,82–84,87,92,96,97,99,108–111,117,122–124] as shown in Table 1 – Characteristics of included studies. No results from unpublished RCTs were found in the clinicaltrials.gov registry. No other records from gray literature databases fulfilled the inclusion criteria. The PRISMA flow diagram provides details of the search process and the selection results (Fig. 1 – PRISMA Flow Chart).

This NMA included 12,356 eyes of 6445 infants. Our primary endpoint, the retreatment rate, was reported by 57 studies. The secondary outcomes, time to retreatment and refractive error, were reported by 21 and 31 studies, respectively. The demographic data are displayed in Table 1. The study cohorts that were included had a mean (SD; number of patients and studies) birth weight of 945.34 g (288.06 g; 6504 patients from 65 studies), gestational age of 26.98 weeks (2,33 weeks; 6518 patients from 66 studies) and postmenstrual age at treatment of 36.97 weeks (7.59 weeks; 5279 patients from 51 studies). The gender distribution was 47.97% female (SD: 9.16; 6282 patients from 55 studies). Cohort follow-up had a mean of 22.03 (SD: 7.48; 5720 patients from 53 studies) weeks.

3.2. Model fit and additional frequentist analysis

The computed measures of fit in the Bayesian analyses for retreatment (Dbar = 126.791, pD = 103.855, DIC = 230.646), time to

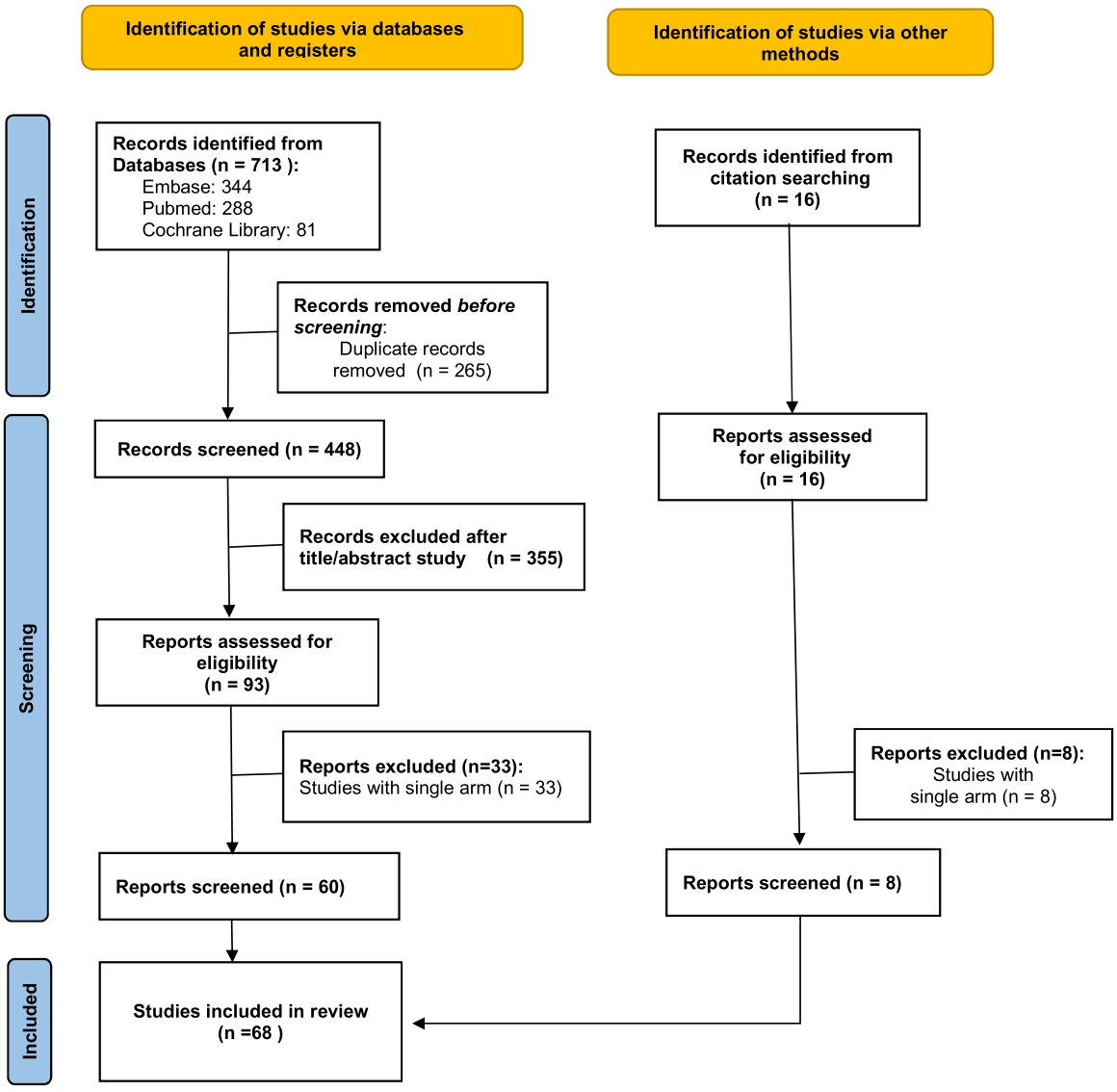

Fig. 1. PRISMA flow chart of all included and excluded studies.

retreatment (Dbar = 52.031, pD = 50.470, DIC = 102.501) and refractive error analyses (Dbar = 65.308, pD = 61.160, DIC = 126.540) indicated a good model performance. The UME residual deviance plots, stem and leverage plots are included in Supplementary Material 2: *Model fit assessment and outlier detection*. The goodness of fit is indicated by the inspection of these plots which displayed a small residual deviance and a good leverage with moderate contribution of data points to a DIC that showed low values. The Bayesian analysis was complemented with a frequentist analysis, and the retreatment rate values were found to be mostly comparable over the analyses. In the analyses of the secondary outcomes, there was also a concordance between the results of both analyses. The league table and forest plot are provided in Supplementary material 3*: Frequentist NMA*.

3.3. Outcomes of pairwise and network meta-analysis

3.3.1. Primary outcome: retreatment rate

The network for retreatment rate comprises 12 nodes (Fig. 2A – Network plot of the included studies). The Bayesian network meta-analysis showed that anti-VEGF agents were similar to laser therapy in terms of retreatment rates, except for conventional infant doses of aflibercept (IVA_ci: RR 3.38; 95% CrI: 1.29, 9.04) and ranibizumab (IVR_ci: RR 2.26; 95% CrI: 1.34, 3.81) which showed significantly increased risk ratios. Among the different doses of IVB, its half of the conventional infant dose (IVB_h), showed the lowest risk of retreatment with a risk ratio of 1.43 (95% CrI: 0.508, 4.03). Conbercept was the intervention with the lowest value of RR for retreatment rate (Fig. 2B - Forest plot). Larger CrI values in Fig. 2B indicate a lower number of studies for their respective comparisons.

These results are also displayed in Fig. 2C – Litmus Rank-O-Gram graph, as well as in Fig. 3A - Radial SUCRA plots, displaying a visual summary of the SUCRA plots comparing all the drugs included in the NMA. Overall, half of conventional infant doses appear to rank better than conventional infant and augmented doses. In particular, for bevacizumab, its half dose (IVB_h) had a better position than the conventional infant dose (IVB_ci), and both of them ranked higher than the augmented dose (IVB_a). Low (IVB_l) and very low (IVB_vl) doses of bevacizumab situated close to the lowest probability ranking. Following this trend, half doses of aflibercept (IVA_h) and ranibizumab (IVR_h) appear to reduce retreatment rates compared to IVA_ci and IVR_ci respectively.

3.3.2. Secondary outcomes: time to retreatment and refractive error

Of the 68 included studies, 8 RCTs and 13 NRIS reported time to

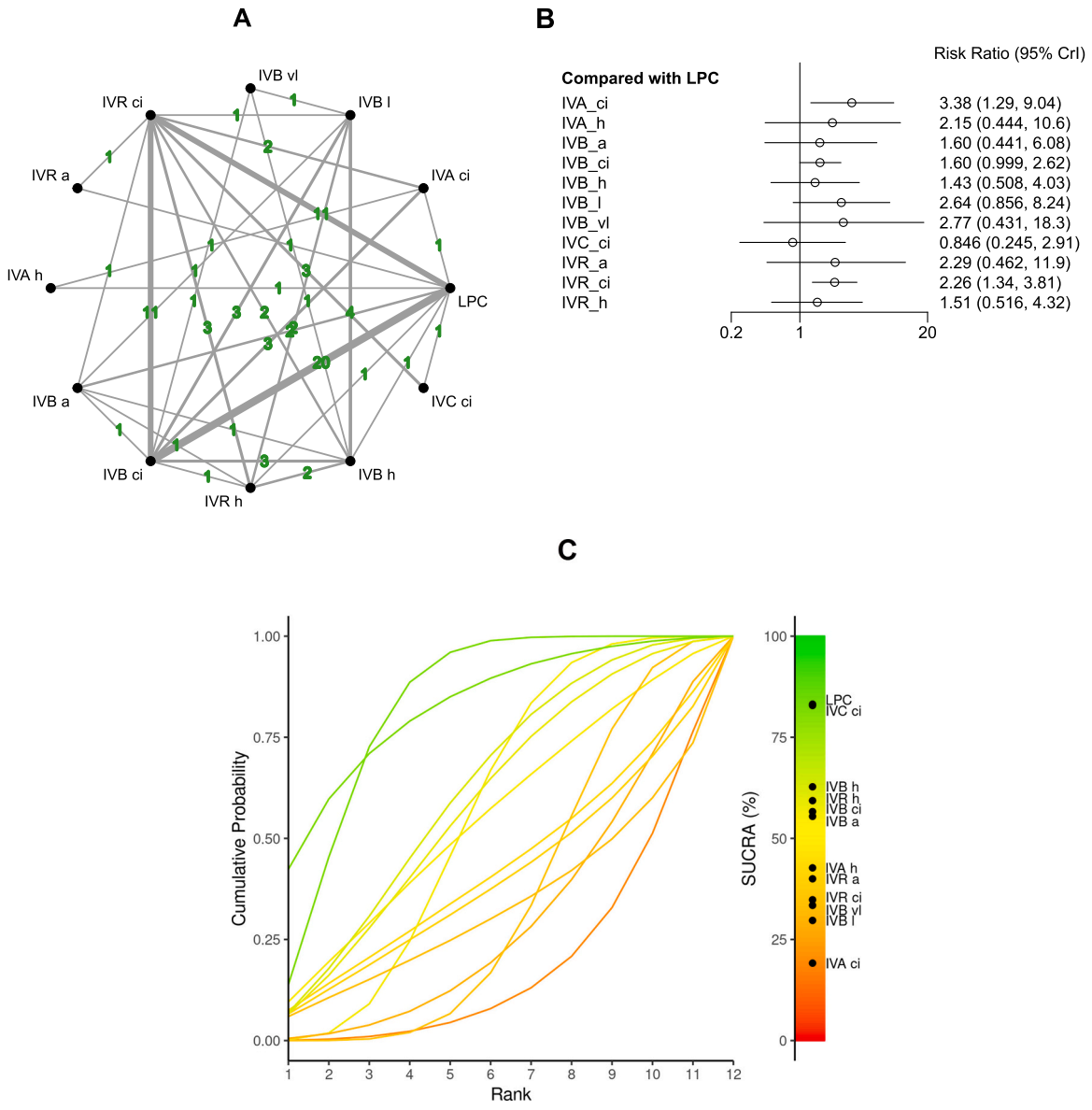

Fig. 2. A. Network plot of the included studies for retreatment outcome, with nodes assigned to each ROP treatment: laser photocoagulation (LPC), intravitreal aflibercept (IVA_h, IVA_ci), intravitreal bevacizumab (IVB_vl, IVB_l, IVB_h, IVB_ci, IVB_a), intravitreal conbercept (IVC_ci) and intravitreal ranibizumab (IVR_h, IVR_ci, IVR_a). Number on the lines indicate number of trials conducted for the comparison. B. Forest plot depicting the effect estimates of retreatment with the corresponding confidence intervals for each anti-VEGF treatment when compared to laser therapy. C. The Litmus Rank-O-Gram presents a cumulative rank-o-gram alongside a 'litmus strip' of the Surface Under the Cumulative Ranking Curve (SUCRA) values acting as a key. Highest values and cumulative curves correspond to a better position in the ranking and are situated nearer the top left. The number of eyes analyzed for each treatment is as follows: LPC, 3622; IVA_ci, 303; IVA_h, 178; IVB_a, 93; IVB_ci, 3934; IVB_h, 254; IVB_l, 257; IVB_vl, 92; IVC_ci, 363; IVR_a, 158; IVR_ci, 2156; IVR_h, 232. The abbreviations used for the dose levels of the anti-VEGFs following the underscore are: conventional infant dose (ci), half conventional infant dose (h), augmented (a), low (l) and very lor (vl) doses.

retreatment data. Results are plotted in Fig. 1 of the Supplementary Material 4. Generally, higher doses were associated with larger times to retreatment. The largest change was noted in the augmented doses of IVB and IVR with means of 14.1 weeks (95% CrI: 6.65, 21.6) and 12.8 weeks (95% CrI: 3.19, 20.9), respectively. Considering the conventional doses of the four anti-VEGF drugs, the mean time following primary injections was 8.65 weeks (95% CrI: 3.52, 13.8) for aflibercept, 6.72 (95% CrI: 2.44, 11.1) for bevacizumab, 3.13 (95% CrI: −0.65, 6.92) for ranibizumab and 2.48 (95% CrI: −3.34, 8.35) for conbercept. Analysis of variance of these values showed significant differences for conventional doses of ranibizumab vs. aflibercept and bevacizumab, as shown in Fig. 1 of Supplementary material 5. Ranking results according to SUCRA for bevacizumab indicated that IVB_a had the highest probability of achieving a longer time period until second treatment, followed by IVB_ci, IVB_h, IVB_l and IVB_vl. Likewise, the IVA_ci ranked higher than IVA_h (Fig. 3B – Radial SUCRA plots).

The refractive outcomes were reported only in 31 out of the 68 included studies (Fig. 2 of the Supplementary Material 4). The Bayesian NMA results were favorable for anti-VEGF therapy, especially for the conventional infant doses of IVB and IVR, which exhibited a significantly better refractive profile than LPC, with a IVB_ci mean difference of 1.67 (95% CrI: 0.705, 2.67) and IVR_ci mean difference 2.19 (95% CrI: 0.782, 3.59). Analysis of variance of these values showed significant differences for aflibercept vs. bevacizumab as shown in Fig. 2 of Supplementary material 5. A smaller amount of SE is considered as a positive outcome and interventions presenting with less probability of myopia were situated at the top of the SUCRA ranking Fig. 3C – Radial SUCRA plots and Fig. 2C of the Supplementary Material 4. Interestingly,

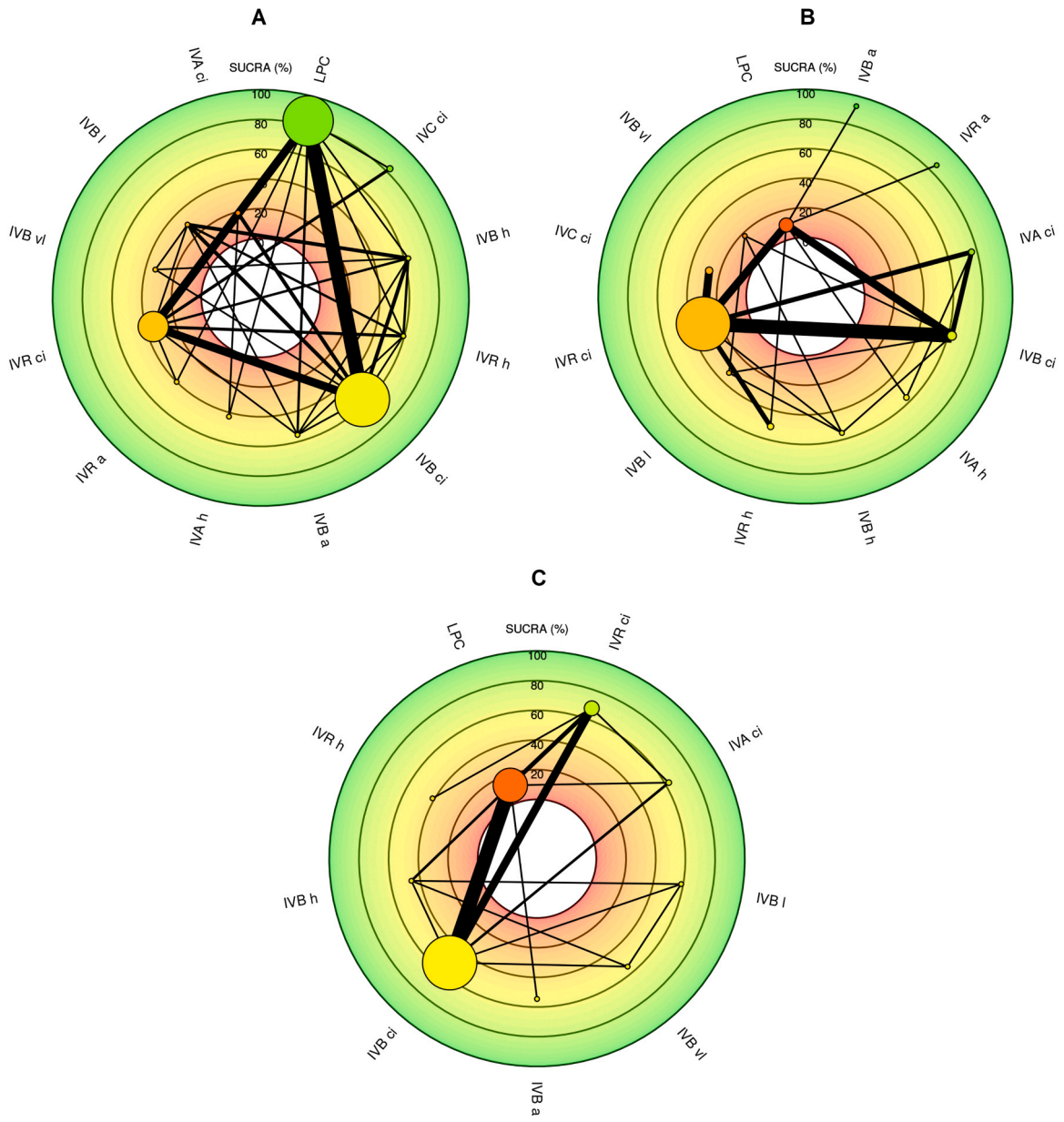

Fig. 3. Radial Surface Under the Cumulative Ranking Curve (SUCRA) plots: Size of nodes represent number of eyes and thickness of lines indicate number of trials conducted. The interventions (LPC, IVA_h, IVA_ci, IVB_vl, IVB_l, IVB_h, IVB_ci, IVB_a, IVC_ci, IVR_h, IVR_ci, IVR_a) are ordered by their SUCRA value clockwise starting at '12 o'clock', with higher SUCRA values indicate better treatments. A. primary outcome analysis – retreatment rate (panel A); secondary outcome analyses: time to retreatment (panel B) and refractive error as spherical equivalent (panel C). The abbreviations used for the dose levels of the anti-VEGFs following the underscore are: conventional infant dose (ci), half conventional infant dose (h), augmented (a), low (l) and very low (vl) doses.

anti-VEGF interventions were grouped inside the middle third of the chart whereas LPC had a markedly different position with a higher probability of having largest negative SE values.

3.3.3. *Confidence in evidence*

The quality of the included RCT and NRIS is assessed in Supplementary Material 6 - *Risk of bias*. Sixty percent of included RCTs had a low risk of bias whilst only 41.5% of NRIS showed moderate risk of bias. Some studies were downgraded to high or moderate risk of bias because of the absence of adjustment for confounders and/or inadequate allocation concealment. Imprecision, heterogeneity, and incoherence were defined for clinically important size of effect for each outcome. The grading of paired comparisons in the network with the CINeMA approach showed low confidence across most of the estimates (see Supplementary Material 7 – *CINeMA grading* for details on how grading for each domain was done). This was mainly due to the imprecision of most of the direct and indirect estimates, which had wider confidence intervals extending on both sides of the axis and were rated as "some concerns" or "major concerns" as well as to the high risk of within-study bias assigned to a certain number of NRIS. Assessment of heterogeneity showed a number of "major concerns" (prediction intervals extending in both directions), while incoherence and indirectness showed a majority of "no concerns".

3.4. *Subgroup analysis of RCTs*

A subgroup analysis including exclusively the RCTs was also performed to assess the risk of retreatment (Supplementary Material 8 – *Bayesian NMA of RCTs)*. The Bayesian network meta-analysis showed that anti-VEGF agents were similar to laser therapy in terms of

retreatment rates. Half doses of bevacizumab (IVB_h) as well as conventional dose of conbercept (IVC_ci) showed the lowest risk with RR values of 0.489 (95% CrI: 0.0116, 12.3) and 0.764 (95% CrI: 0.0068, 87.0), respectively. The conventional and augmented doses of bevacizumab demonstrated higher risk than the half dose, with a RR of 0.849 (0.119, 6.58) and 3.83 (0.235, 81.1) respectively. As for the main analysis, larger CrI values, in particular for conbercept, indicate a smaller number of RCTs available for analyses.

3.5. Subgroup analysis of effect modifiers

A meta-regression was performed to assess whether the risk ratios of retreatment rates were varied consistently across the range of birth weight, gestational age and postmenstrual age at treatment values. The corresponding graphs are shown in the Supplementary material 9 – *Meta-regression analysis*. No statistically significant moderating effect was found along the range of these clinical variables for any of the treatment comparisons in which the comprised number of studies allowed the statistical analysis.

4. Discussion

Laser therapy is considered the standard treatment for ROP but the use of anti-VEGF agents has increasingly been recognized.[4] Consensus is complicated as there is a limited number of RCTs evaluating the long-term outcomes following anti-VEGF treatment as well as the preferred agent and its appropriate dose. Furthermore, a substantial amount of the available evidence is derived from observational studies which offer a more real word evidence but usually have a retrospective design with small samples size. This NMA is the first to obtain information of distinct anti-VEGF agents from direct and indirect comparisons, including conbercept, which was recently incorporated to the therapeutic armamentarium against ROP[2] and not included in previous meta-analyses.[7,93,94,112,126] Moreover, we also aimed to provide estimates of intervention hierarchies for different dose levels of anti-VEGF agents. A relevant advantage of the NMA technique is the option of quantitatively addressing both direct and indirect evidence of several competing interventions, and strengthening inference concerning their relative efficacy.[16]

Retreatment rate is commonly taken as a measure of the relative efficacy of interventions in ROP. Our results from the main analysis show a similar probability of receiving additional treatment when comparing anti-VEGF injections and laser therapy, except for aflibercept and ranibizumab at conventional infant doses, which had an augmented risk. These findings are comparable to those of a recent NMA showing higher retreatment incidence in the ranibizumab arm.[7] Since RCTs represent the highest quality of evidence, we performed a subgroup analysis of RCTs only which showed that anti-VEGF drugs were similar to laser therapy in terms of retreatment rates. Another meta-analysis, entirely of RCTs only, reported similar rates in its overall analysis[112] while the results of other meta-analysis[94] of mixed RCTs and NRIS studies significantly favored the laser group.

To date, bevacizumab has been generally used in a dose of 0.625 mg (half of the dose administered intravitreally in adults for ocular neovascular diseases). Similarly, aflibercept and ranibizumab are often used at doses of 1 mg and 0.25 mg, respectively. Despite the recognized efficacy of this therapeutic approach, recent research has addressed whether using half-adult dose may result in overtreatment of many infants,[12,22,103,118,119,122,124] as the impact on neurological[81,85] and macular[61] development remains of concern. Following this line, some studies showed that the size-adjusted bevacizumab dose in neonates should be 0.4 mg,[100] and ROP can regress with doses of 0.031 mg.[120] The NMA technique allows the combination of data from multiple trials, which otherwise would be difficult to compare. Indeed, this NMA differs from previous meta-analyses[7,93,94,112] in that we considered differences in dose levels for each anti-VEGF agent. For instance, in the NMA of Chang *et al*,[7] the aflibercept group included results of 4 studies using two different doses (1 mg[21,96,111] and 0.4 mg[105]) whilst our work distinguished studies dosing with 1 mg[21,22,40,74,96,110,111] from those of 0.4 mg,[22,105] and added 196 eyes to the sample analyzed.

In the ranking of interventions based on the forest plot and SUCRA analyses, the likelihood of retreatment appears conformed by four clusters based on differences of their risk ratio values and their cumulative probability estimates, respectively. It appears clear that the anti-VEGFs efficacy in terms of retreatment attained by the reduced doses are reasonably close to the obtained with conventional doses. Concerning bevacizumab, IVB_h (0.25–0.5 mg) seems to be discretely superior to IVB_ci (0.625 mg) and both appear to be a preferable option vs. IVB_a (0.75, 1.25 mg). Similarly, IVA_h and IVR_h had a reduced likelihood of retreatment compared to IVA_ci and IVR_ci. The “low” and “very low” anti-VEGF doses have been only tested with bevacizumab and the latter was the lowest ranked. A moderate reduction of dose may therefore maintain the rate of retreatment. This is also supported by some authors who considered that we could be overtreating premature infants with severe ROP. Since an avascular peripheral area of retina may remain undeveloped after intravitreal injections, especially after higher doses, the ideal anti-VEGF regimen would prevent pathologic neovessels formation while allowing retinal revascularization.[103] Finally, regarding conbercept, it was categorized on the ~~t~~op of the SUCRA rank. A unique arm study[12], excluded from our NMA, revealed that 0.15 mg of conbercept, a lower dose than the conventional infant dose of 0.25 mg, resulted in a 15.8% retreatment rate, similar to the reported values in the conventional dose studies.[46,66,121] This suggests that a reduction in the dose of conbercept may also maintain its efficacy. Conbercept has a broader binding to VEGF family members and an additional domain 4 of VEGFR2 compared to other anti-VEGF drugs, thus allegedly enhancing its affinity and half-life. Nevertheless, the number of conbercept studies is considerably inferior to those of the other anti-VEGF drugs, and, given its newness, drug’s pharmacokinetics, clinical efficacy, and best practices in ROP application have yet to be ascertained.[67] Altogether, these nuances in the rank order of interventions need to be interpreted with caution but give support to the assumption that a controlled dose reduction do not necessarily translate into a decreased efficacy, which is concordant with reports from other authors.[54]

Time to retreatment is also a commonly used indicator of the relative effectiveness of the therapeutics of ROP. When considering dose scaling, the forest and SUCRA plots showed that the eyes retreated with higher anti-VEGF doses presented with a longer time interval elapsed before secondary treatment. This was particularly unequivocal for bevacizumab; whose different dose levels appear arranged in a decreasing sequence with lower doses holding a shorter interval until a further course of retreatment is needed. These estimations coincided in both NMA and variance analysis. The time interval until second therapy is needed is somewhat determined by the time in which the effect of anti-VEGF present in the vitreous cavity wanes off. Consequently, it seems plausible that lower doses will have a shorter duration of effective drug concentration, and retreatment would take place more rapidly in those cases where it is needed.[12] For that reason, dose scaling should be cautious as it is imperative to ensure a threshold concentration exerting the desired therapeutic effect in each case. On the other hand, retreatment occurs earlier following intravitreal ranibizumab than after aflibercept or bevacizumab at conventional doses, a result previously noted in part by other meta-analysis.[7] This can be explained by different pharmacological characteristics of the anti-VEGF drugs, which play an important role in their vitreous distribution and elimination, and thus in their action on decreasing the rate of pathological production of VEGF.[28] For instance, these agents differ in chemical structure, size and half-life, with ranibizumab’s having the shortest half-life and subsequently its intravitreal effect may be shorter. This raises interest in the differential ocular and systemic effects of the different antiangiogenic drugs, which needs further investigation.[75,103] Finally, laser intervention appears as

the shortest time to retreatment. Only minimal amounts of new VEGF is produced by the ablated peripheral retina if there is an adequate confluent laser spot density.[39,63] In cases of areas inadvertently skipped by laser, signs of treatment failure manifest promptly and the time to retreatment (frequently given for incomplete regression instead of reactivation) is typically shorter in comparison with anti-VEGFs as previously stated.[78] Our data should be integrated with other factors also implicated in the time to retreatment such as the systemic conditions of the infant, like basal weight [56,76] or higher VEGF loads in aggressive ROP in order to choose the most adequate dose in each case.[5]

Abnormalities of the anterior segment resulting in high myopia were initially seen in the eyes of infants enrolled in the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP) study who received retinal ablative therapy.[77] Although still speculative, there is a biological plausibility for the higher rates of myopia after laser therapy. The destroyed peripheral retina not only induces visual field deficits but also modifies local growth factors, resulting in abnormalitis of the anterior segment, such as greater corneal curvature, long axial length or high lens power.[73,95] By contrast, it has been established that the primary treatment with anti-VEGF agents produced less myopia compared with laser,[53,63,93,113] including the results of the 2-year outcomes of ranibizumab versus laser therapy for the treatment of very low birthweight infants with ROP (RAINBOW extension study) which also reported lower prevalence of high myopia in the ranibizumab 0.2 mg arm.[70] In this NMA, we replicated and expanded these findings. Thus, in the SUCRA plot, laser therapy appears as the intervention modality at the bottom of the column of probabilities linked to refractive error and placed at a distance to the estimates found for anti-VEGFs which form a cluster.

To a great extent, a well-balanced profile between efficacy and safety is of great importance in the election of the best therapeutic option for ROP. Laser has demonstrated robust efficacy but reported adverse events and its difficult application, especially in cases of poor pupillary dilation or media opacities, should not be disregarded.[44] Premature infants may also experience side effects of general anesthesia, necessary to undertake this procedure.[45] This is outweighed by the advantages of anti-VEGF therapy such as easier administration, fast regression of neovascularization and less myopia.[38,114,115] Results from this NMA support the sustained efficacy of the reduced anti-VEGF doses and reinforce the rationale for their use as its related side effects would also be decreased. Indeed, although retinal vascularization can be impeded after antiangiogenic administration, high doses may produce more vascular arrest than the lower doses.[20] In relation to this, Stahl *et al* signaled that low doses can achieve a fully vascularized retina and suggested that repeating a low dose in retreated patients could be preferable to systematically employing a starting high dose.[103] Hence, an ideal equilibrium of anti-VEGF treatment would prevent pathologic neovascularization after reaching a minimum effective concentration level, while allowing physiological vessel growth and reducing local and systemic toxicity. Further dose finding studies are certainly needed, along with the determination of baseline risk factors with a pivotal emphasis in individualizing treatment decisions.

This NMA has some limitations. The study was powered for an effect in the overall population, and we combined RCTs and NRIS with heterogeneity among studies and high risk for confounding factors. Heterogeneity was an awaited feature of this NMA with a number of potential sources. Heterogeneity was the reason to use a random-effect model to minimize this limitation. Study populations appear comparable in terms of means of birth weight, gestational age and postmenstrual age at treatment and no significant association was found between the value ranges of these effect modifiers and the risk ratios of retreatment rates for those treatment comparisons with a sufficient number of studies. Another limitation is the grouping convention of different dose levels of anti-VEGFs to assure the feasibility of the NMA which yielded heterogeneity within the intervention nodes. Since many NRIS have a retrospective design, data analysis is based on routine clinical documentation and the risk of bias is high. A weakness of the included RCTs is that therapeutic options were unmasked, as the intrinsic characteristics of the disease and its current available therapies cannot allow the possibility of making them indistinguishable, and the systemic circulation of the anti-VEGF may bias the effect observed on the laser-treated contralateral eye. Another shortage is that some of the interventions were assessed by a low number of the existing studies. Further studies comparing multiple intervention groups and contemplating different intravitreal dose levels are needed as well as long term studies evaluating additional outcomes like visual acuity or adverse events. In addition to this, differences in disease severity were not considered in many of the included studies. Thus, more well-designed studies are required to investigate the effects of different intravitreal doses of anti-VEGF agents on different ROP zones and stages as well as their systemic side effects. On the other hand, a strength of this study was the inclusion of the different ROP treatments, including conbercept. The large amount of analyzed eyes offers a robust statistic power and a realistic approximation of treatment effects in light of the existing evidence. Finally, the approach to establish a hierarchy of treatments based on the relative intervention effect estimates may be of interest in the planification of future clinical studies. Our results provide information that could be integrated with other clinical features in order to determine the best effective anti-VEGF dosing regimen and the optimal follow-up time in each case.

5. Conclusions

Laser and antiangiogenic therapies play an important role in combating ROP and show an acceptable benefit-risk profile. Current available anti-VEGF agents bring us with some benefits in respect to laser such as a lower risk of myopia, but some antiangiogenic-related undesirable effects remain of concern and the precise dose level is yet to be determined. This NMA found that lowering conventional anti-VEGF doses in a controlled manner did not result in a decreased efficacy; however, since lower doses may contribute to an earlier drug clearance and a shorter time to retreatment, additional baseline factors should be considered to provide an individualized approach. Overall, the emerging evidence that low drug doses may be efficacious while reducing ocular and systemic impact may contribute to a new paradigm in the treatment of this sight-threating condition.

6. Method of literature search

Two reviewers (JLO and AOS) conducted a systematic literature search. The search strategy was revised by an experienced librarian of the Medicine Library of the University of Valencia. In case of any discrepancy, a third and fourth reviewer (PM and IPC) helped with decision-making. Databases queried were EMBASE (2005 to June 2023), PubMed (2005 to June 2023), and Cochrane Library (June 2023). The clinicaltrials.gov registry was searched to look for any RCT with results reported but not formally published. Gray literature databases were also searched. Medical subject headings (MeSH) and free text search terms related to ROP were used. Relevant articles were identified, and appropriate keywords were extracted and included in the next search iteration until all pertinent search terms were captured. The reference lists from included studies and studies that were excluded after full text assessment were also examined to identify relevant reports. There were no restrictions on language, location or journal of publication. The database search was completed in June 30, 2023. Search strategies for each database are indicated in Supplementary material 1*: Search strategy*.

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CRediT authorship contribution statement

José L. Ortiz: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Esteban Morcillo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Isabel Pascual-Camps:** Visualization, Validation, Supervision, Software, Methodology, Conceptualization. **Honorio Barranco:** Visualization, Validation, Supervision, Methodology, Conceptualization. **Pablo Martorell:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Investigation, Formal analysis. **Amparo Ortiz-Seller:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.survophthal.2024.02.005.

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