LITERATURE REVIEW

EFFICACY OF INTRAVITREAL ANTI VASCULAR ENDOTHELIAL GROWTH FACTOR INJECTION COMPARED TO FOCAL THERAPY IN PEDIATRIC PATIENTS WITH COATS DISEASE

Alia Nessa Utami[1], Julie Dewi Barliana[2]
[1] Department of Ophthalmology, Faculty of Medicine University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta
2 Pediatric Ophthalmology Division, Department of Ophthalmology, Faculty of Medicine University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta
Email: alia.nessa@yahoo.com

ABSTRACT

Introduction: *Coats disease is a retinal vascular disorder that may lead to progressive exudative retinal detachment. The standard regiment of treatment is focal therapy. However, its effectiveness may decrease when more than two quadrants of the retina exhibit vascular abnormalities. Thus, recent studies tried to use anti vascular endothelial growth factor (anti-VEGF) as therapy for the vascular problems.*

Aims: *Comparing the efficacy between anti-VEGF injection and standard therapy regiment such as focal laser therapy.*

Methods: *Literature searching was conducted through PubMed, ScienceDirect, Google Scholar, ProQuest, and SpringerLink. Search terms included "Coats' Disease" and mesh terms of "Anti-VEGF". The efficacy is assessed based on Best-Corrected Visual Acuity (BCVA) and improvement in fundus manifestations.*

Results: *All of the studies that conducted primary intravitreal anti-VEGF treatment were followed by necessary ablative treatment. These studies, such as by Yang Q and Zheng XX, et al. showed remarkable improvements in both visual acuity and anatomical outcomes. Laser therapy also gained satisfactory result in upgrading clinical stages, even though some complications including subretinal fibrosis, cataract, and vitreous hemorrhage were reported. A comparative study by Ray R, et al. noted that group undergoing anti-VEGF might require longer treatment sessions despite possible benefits.*

Conclusion: *Anti-VEGF agents can be used as neoadjuvant in standard therapy. It did not reduce the time for full treatment, but the resolution of disease was seen in the most severe cases treated with combination therapy.*

Keywords: *anti-VEGF, Coats disease, focal therapy*

INTRODUCTION

Coats disease is an idiopathic progressive retinal vascular disorder, usually found in young males, which is characterized by retinal telangiectasia, intraretinal, and subretinal exudation.[1] This may lead to progressive exudative retinal detachment and subretinal lipid deposits.[1,2] Although many eyes with Coats can be stabilized, more advanced cases may progress to complete retinal detachment and frequently require enucleation.

A study in the United Kingdom revealed 55 new cases of Coats disease diagnosed through 12 months of an active surveillance program.[2] A study in Indonesia revealed that Coats disease is the most frequent cause of exudative retinal detachment in pediatric patients, accounting for 50% of the cases, despite the difficulty in screening.[3] The case was mostly found in the 11-15 year age group with a ratio of 3:1 of male and female new cases.[3,4] Most patients in Indonesia were treated with a combination of laser photocoagulation, cryotherapy, and vitreoretinal surgery.[3]

The standard regiment of treatment mainly revolves around vascular ablation using laser photocoagulation or cryotherapy, or later on will be referred as standard focal therapy.[4–6] However, the effectiveness of standard thermal laser photocoagulation may decrease when more than two quadrants of the retina exhibit vascular abnormalities.[4] Therefore, more advanced treatment emerges in a clinical setting, with anti-vascular endothelial growth factor (anti-VEGF) that has partaken a role in subsiding the vascular problems of Coats disease.[4,7] However, recent studies on the benefit of anti-VEGF still showed conflicting results which proved that ocular angiogenesis is a complex mechanism involving multiple pro and antiangiogenetic factors that integrate with other pathological changes.[4,8] Thus, this literature review aims to evaluate the efficacy and effectivity of anti-vascular endothelial growth factor injection as the main therapy of Coats disease, compared to standard focal therapy, such as laser photocoagulation and cryotherapy.

METHODS

Literature search and selection

Literature searching was conducted using five online databases (PubMed, ScienceDirect, Google Scholar, ProQuest, and SpringerLink). Search terms included a combination of main keywords: "Coats' Disease" and mesh terms of "Anti-VEGF", which include bevacizumab, ranibizumab, or other kinds of anti-VEGF drugs. We also included focal therapy, such as laser therapy and cryotherapy at research terms. Reference lists of each study were also assessed for potentially relevant sources.

Articles were included if written in English and full-text available. All the studies have to fulfill the following criteria: (1) subjects included children below 18 years old, or have separate analysis on children subjects with Coats Disease, (2) studies included must be in the last 10 years, (3) studies should either have anti-VEGF injections or have standard therapy as the main treatment, and (4) minimum follow-up of three months. We excluded case reports and case series with less than three patients, studies with fair treatment of both modalities or clear

combined treatment since the beginning of diagnosis, and studies that observed primarily the effect of surgical management such as scleral drainage or pars plana vitrectomy. All studies included in this review were rated based on the Oxford Center of Evidence-Based Medicine 2011 Level of Evidence and were evaluated for validation using the pre-set validity assessment tool for case series. The process is shown in figure 1 below.

Data processing

The information extracted from each study included the authors of each study, the year study was reported, the number of subjects, the treatment modalities for the subjects, and outcome of the studies, including BCVA, fundus manifestations such as retinal detachment and telangiectasia, and the complications during treatment. Efficacy is assessed based on Best-Corrected Visual Acuity (BCVA) and improvement in fundus manifestations.

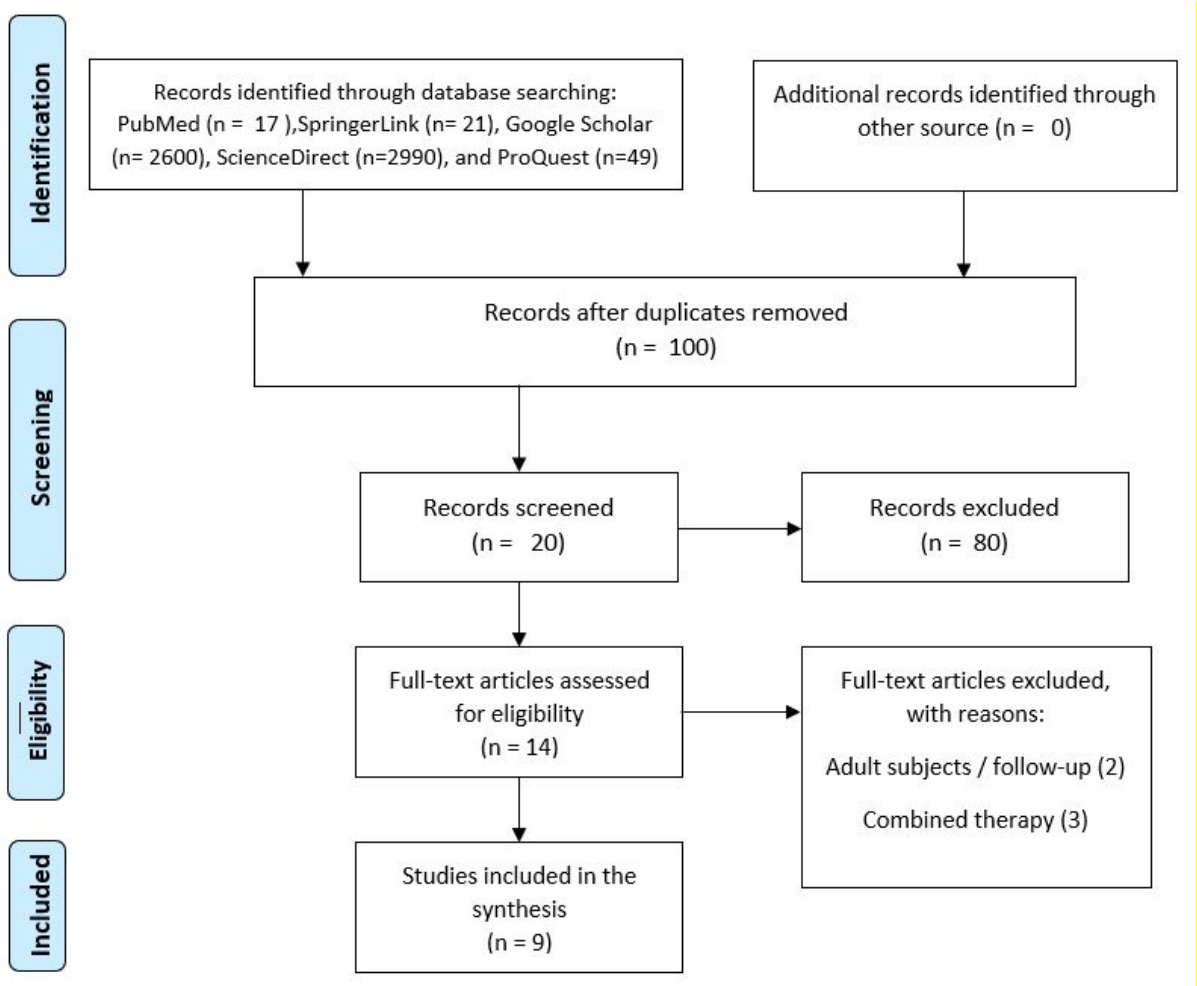

Figure 1. A literature search using PRISMA flow chart

RESULTS

A total of nine articles using relevant search terms in various databases are included in this review. These articles are mostly retrospective reviews of Coats disease cases, with treatment using various type of anti-VEGF and standard therapy. A flowchart of the article selection process is shown in Figure 1.

The characteristics of the eligible studies are summarized in Table 1. A total of 69 eyes mainly focused on anti-VEGF injections, and 96 eyes used standard focal therapy were included in this study. The outcome measured to objectively assess the success of treatment was the best-corrected visual acuity (BCVA) and anatomical improvements, such as telangiectasia quadrants, exudate condition, and the presence of exudative retinal detachment. Telangiectasia quadrant and exudate condition were assessed using fundus photograph in 100% of screened studies.

Several studies assessed the pre and post-treatment BCVA. Lin et al. reported visual acuity improvement in two out of three patients reported in the case series.[9] Yang Q and Zheng XX et al. used combination therapy, and both showed a significant improvement in BCVA with p-value of <0.001 and 0.006 (at week 6), respectively.[10,11] Meanwhile, another study by Li et al., who also use combination therapy only showed partial improvement.[12]

A study by Shapiro MJ et al. using green diode laser ablation therapy showed a varied range of final BCVA.[13] Four (29%) of 14 eyes had 20/50 or better visual acuity, 21% of total subjects had 20/60 to 20/200 visual acuity, 36% of 14 eyes had 20/400 to light perception visual acuity, and 14% of total subjects had no light perception acuity.[13] Standard therapy was also used by Mulvihill A et al., who did not specify their result but stated that 32% of the eyes showed an improvement, 41% have a stable BCVA, and the rest showed a worsening condition.[14] The last study that gives the BCVA result is the study by Levinson JD et al., who also uses standard therapy and found that the greatest improvement is on the number of subjects with visual acuity range 20/60 to 20/200, increasing from 16.7% to 30%.[15] However, the majority of subjects' VA was still 20/200 or worse, comprised of 8 patients before treatment to 7 eyes after treatment.[15]

The anatomical results were described in most of the studies. Ray R, et al. compared a set of patients receiving intravitreal bevacizumab combined with laser or cryotherapy, matched with a set of patients receiving solely standard therapy.[1] The study showed that out of two patients with initial bevacizumab treatment, one patient had minimal improvement on retinal detachment, and the other one did not show any resolution of SRF despite improvement in visual acuity.[1] Notable improvement was seen in one of the patient which underwent bevacizumab plus laser and cryotherapy, showed resolved exudative retinal detachment after

two sessions.[1] The number of treatment sessions required differed significantly (p=0.002) between the two groups, with eyes treated with bevacizumab requiring more total treatments (4.3 sessions), compared to standard focal therapy (2.6 sessions).

Ramasubramanian, et al. did a retrospective analysis of eight patients undergoing bevacizumab intravitreal injection following standard therapy.[8] Anatomical outcome showed that significant resolution of exudates managed to happen in 75% of the subjects (6 patients), with the other two having partial exudate resolution. Half of the subjects had significant subretinal fluid resolution, while the other had partial resolution.[8] Notable complications, including vitreoretinal fibrosis and tractional retinal detachment, were happening in 50% and 38% of total subjects respectively.[8]

Lin CJ, et al. conducted a prospective, interventional, and non-comparative case series of three eyes diagnosed with Coats disease.[9] All eyes received only intravitreal bevacizumab injection as the primary treatment every 4 weeks until the subretinal fluid completely reabsorbed. Patient also received ablative procedures, including cryotherapy after subretinal fluid completely resolved. After treatment, one patient had improved visual acuity to 20/100 and complete resolution of submacular exudation for one year, another had remarkable resolution of exudative retinal detachment on B-scan sonography, and one patient had improved visual acuity to 20/200 with resolved exudative retinal detachment and decreased subretinal lipid.[9]

Yang Q, et al. conducted a prospective, non-controlled clinical trial on patients younger than 16 years of age undergoing intravitreal ranibizumab injection.[10] Patients were solely treated with intravitreal ranibizumab monthly in the first three months as initial treatment, which was combined with another ablative therapy as needed. After 9.1 months of follow-up, there were resolution of subretinal fluid (n=14, 100%), exudation (n=14, 100%), and a regression of telangiectasia (n=14, 100%). It must be noted that there were two patients with vitreoretinal fibrosis after treatment, even though it was not sure ranibizumab was the agent which aggravated the complication.[10]

A retrospective review of 14 consecutive children eyes was conducted by Zheng XX, et al.[11] All patients were treatment-naïve, and underwent intravitreal bevacizumab injection, as stated on table 1. Follow-up treatments, such as laser photocoagulation, cryotherapy, and reinjection, were administered as needed. Differences in BCVA were significant even at week 12 (p=0.005) and 24 (p=0.005) after baseline. After a mean of 9.1 months, a resolution of the subretinal fluid, exudation, and telangiectasia were observed in all the patients, as mentioned on table 2 below.[11]

Li, et al. did a retrospective, non-controlled clinical study on 17 patients.[12] Patients were given ranibizumab with a single dose of 0.05 mL. Patients were then either undergoing intravitreal injection alone, injection combined with retinal photocoagulation, or combined with cryotherapy.[12] Result showed significant difference between preoperative and postoperative retinal detachment heights according to 2-related samples Wilcoxon ranked test (p=0.000). There were no ocular or systemic complications observed. There was no statistically significant difference between preoperative intraocular pressures (11.71 ± 2.95 mmHg) with postoperative intraocular pressures (11.06 ± 0.54 mmHg).[12]

A significant improvement in retinal detachment (>92% of the subjects) can also be seen in studies observing the effects of laser therapy for Coats disease, such as by Shapiro MJ, et al.[13] Retrospective and interventional case series was done by Shapiro MJ, et al. to review the effects of green diode laser in treatment of pediatric coats.[13] All thirteen patients (14 eyes) were diagnosed, managed, and treated by 1 physician. Overall, 13 (93%) eyes reached a positive end point after laser treatment alone and had no active exudation after treatment. 3 eyes (21%) had normal foveal reflex at the end of the treatment, while the other had mild atrophy (21%, n=3), moderate atrophy (21%, n=3), and subretinal fibrosis (21%, n=3).[13]

Mulvihill A, et al. conducted a prospective population-based study of Coats disease through the British Ophthalmic Surveillance Unit (BOSU).[14] There were 55 completed baseline questionnaires for eligible cases of Coats disease, as stated on table 1. There was an improvement in staging of 16 eyes (39%) treated with laser, whereas 24 eyes (59%) remain unchanged.[14] Intravitreal injections of anti-VEGF were used as adjunctive therapy in small number of patients (seven injections to four eyes) with no marked difference in outcomes. The most notable feature is the marked improvement in staging. Before treatment, the mildest staging was stage 2A, whilst after primarily laser therapy, nine eyes (22%) were classified as stage 1.[14]

Different type of laser treatment showed varied result. Levinson JD, et al. conducted a retrospective consecutive case series on 17 eyes (16 patients) undergoing yellow laser photocoagulation treatment (577-nm wavelength).[15] Patients were treated exclusively without the use of cryotherapy or bevacizumab. Eyes with retinal detachment required a mean of 2.86 treatment sessions versus a mean of 2.22 sessions in eyes without retinal detachment (p=0.1264). After treatment, two eyes had normal appearing macula (11.7%) and full vision restoration, while the twelve eyes also had subretinal fibrosis.[15]

In total, only 33.3% (n=3) out of the studies reported complications during treatment, namely vitreoretinal fibrosis, tractional retinal detachment, cataract, and vitreous hemorrhages.

Among those, vitreoretinal fibrosis became the most commonly found complications, followed by tractional retinal detachment.[8,11,15] The details are summarized in table 3.

DISCUSSION

Treatment of Coats' disease aims at improving the adhesion between the neurosensory retina and its underlying retinal pigment epithelium, also at preserving the macular function.[16,17] Cryotherapy and laser photocoagulation have been performed with beneficial effects in cases of more peripheral situated leakages. However, both techniques were also reported to have a poor prognosis in patients with an advanced stage of Coats disease, the main signs being massive retinal exudation or serous retinal detachment.[10] Thus, the hypothesis of using anti-VEGF agents as therapy modalities that will have effects in a complex cascade of angiogenesis emerged.[17,18]

In this study, none of the studies showed a particular challenge/rechallenge effect, because mostly the studies used standardized protocol of the administration of anti-VEGF agents or laser photocoagulation. Withdrawing and re-administrating the drugs in this phase is not ethical, thus the absence of such a method. In order to ensure the subjects' safety, all studies had laser and cryotherapy treatment as an adjuvant at least during the follow-up period as active telangiectasia should still be treated with laser photocoagulation.[1] Further follow-up suggested that despite the addition of bevacizumab intravitreal injection, subjects still needed a significantly longer time to have a full recovery from their active telangiectasia (8.1 months) compared to standard therapy (5.1 months).[1] Around 33.3% of the studies which monitored the effect of anti-VEGF injection stated the number of injections needed was within one until five times, which may contribute to the longer follow-up period.[11,12]

In 100% of the studies we screened, most subjects were at stage ranging from 2B to 3B. Standard treatment consisted of laser photocoagulation and cryotherapy are effective at stage two or stage three of Coats disease without severe detachment.[19] Repeated treatments in these stages are reported to be effective against telangiectasia and aneurysms.[4,19] The increasing use of anti-VEGF, such as ranibizumab and bevacizumab intravitreal injection, is usually targeted at patients in stage 3A or 3B and have shown a partial improvement in stage four patients when uses as neoadjuvant.[19]

About 33.3% of the studies revealed significantly better visual acuity after the administration of anti-VEGF agents.[9–11] This was due to improved resolution of subretinal fluid and exudation. Besides, the patient also reportedly has a regression of telangiectasia after injections.[10] After retinal re-attachment or most of the subretinal fluid was absorbed with the

help of anti-VEGF agents, the patient underwent retinal photocoagulation or retinal cryotherapy. Compared with traditional therapies, this approach is deemed more simple, safe, and effective.[12] On the contrary, 33.3% of the studies reported the effect of vitreous traction after the administration of anti-VEGF.[8,11] The hypothesis surrounding the outcome noted that this was due to rapidly decreased levels of VEGF, which further caused accelerated fibrosis and posterior hyaloidal contraction.[20] Longer follow-up time is needed to ensure the ongoing pathology of this complication, especially since it is proposed that vitreoretinal fibrosis is a natural occurrence during Coats disease.[21,22]

The most consistent finding throughout the studies was that exudative retinal detachment and SRF, especially in more advanced stages (stage 3A or later), was resolved after intravitreal injection.[1,9,11,12] In one study by Ray R, et al., one patient showed marked reduction of total exudative retinal detachment after treatment sessions including bevacizumab, laser, and cryotherapy.[1] Macular exudates were completely absorbed after a prolonged follow-up, although it does not entail that visual acuity can be rescued.[20] To further enhance the magnitude of the effect; a large, multi-center, and prospective clinical trial is needed to see the effect. The problem that it may still need to be combined with standard focal therapy to combat telangiectasia remains.

Generally, new forms of laser photocoagulation are also emerging to help the therapy in earlier stages. Yellow laser has been suggested to be the most effective for vascular structures. Laser photocoagulation can be used effectively in Coats disease when it is directed at vascular abnormalities.[13,15] In addition to the closure of aneurysms and vessel walls to impede leakage, a laser may also decrease VEGF production after retinal ablation.[13]

Our data showed that laser photocoagulation alone might help with the absorption of subretinal fluid and exudates. Besides, the staging of 39% of patients improved with focal treatment alone.[13–15] Although vision usually does not improve with this focal therapy, structural improvement is possible, and virtually all eyes can be saved.[14] 98% of the eyes treated mainly with standard focal therapy showed stabilization in later stages. As consequence, the disease stage at diagnosis is an important prognostic factor in this series.[14]

The studies that we analyzed noted that anti-VEGF agents did not reduce the time for full treatment, but the resolution of disease was seen in the most severe cases treated with a combination of anti-VEGF and laser ablation, whereas the matched controls failed therapy with ablative therapy alone.[1,15] We concluded that this supports the use of anti-VEGF agents as neoadjuvant in standard therapy. However, as a primary choice of modality, this still needs further conduct of research. The follow-up study should at least have a similar objective way to

quantify the function of the retina, for instance with the use of OCT and fluorescein angiography, not merely on fundus photography alone. For validity purposes, to prove the efficacy of these agents as main therapy, anti-VEGF injections should be used as sole treatment in the first three months, albeit the difficulty it may face due to the natural course of Coats disease.

CONCLUSION

Intravitreal anti-VEGF injections had positive effects on the visual acuity, resolution of exudative retinal detachment, and retinal exudate changes in patients with Coats disease. This result was obtained through studies, which mainly persisted having standard focal therapy as adjuvant modality during follow-up period. The differences in treatment regimen, length of follow-up and severity of disease made it difficult to postulate an agreeable statement on the effect of anti-VEGF injection.

Laser photocoagulation therapy had favorable result, especially in patients with stage 2 or stage 3 Coats disease. Patients that were diagnosed at later stage of Coats disease showed trends of better overall prognosis of result with the help of intravitreal anti-VEGF injections, which further cemented the hypothesis of anti-VEGF's role as adjuvant therapy. In order to claim the efficacy, a large, prospective, and multi-center clinical trial on this topic is still needed.

REFERENCES

1. Ray R, Barañano DE, Hubbard GB. Treatment of Coats' disease with intravitreal bevacizumab. *Br J Ophthalmol*. 2013;97(3):272-277. doi:10.1136/bjophthalmol-2012-302250
2. Morris B, Foot B, Mulvihill A. A population-based study of Coats disease in the United Kingdom I: Epidemiology and clinical features at diagnosis. *Eye*. 2010;24(12):1797-1801. doi:10.1038/eye.2010.126
3. Irfani I, Kartasasmita AS. Pediatric Retinal Detachment in Indonesia: Clinical Characteristics, Risk Factors, and Treatment Outcomes. *Open J Ophthalmol*. 2017;07(04):249-255. doi:10.4236/ojoph.2017.74033
4. Sigler EJ, Randolph JC, Calzada JI, Wilson MW, Haik BG. Current management of Coats disease. *Surv Ophthalmol*. 2014;59(1):30-46. doi:10.1016/j.survophthal.2013.03.007
5. Mrejen S, Metge F, Denion E, Dureau P, Edelson C, Caputo G. Management of retinal detachment in coats disease: Study of 15 cases. *Retina*. 2008;28(3 SUPPL.):26-32. doi:10.1097/IAE.0b013e31816b3158
6. Char DH. Coats ' syndrome : long term follow up. *Br J Ophthalmol*. 2000;84:37-39.
7. Zhao Q, Peng XY, Chen FH, et al. Vascular endothelial growth factor in Coats' disease. *Acta Ophthalmol*. 2014;92(3):225-228. doi:10.1111/aos.12158
8. Ramasubramanian A, Shields CL. Bevacizumab for Coats' disease with exudative retinal detachment and risk of vitreoretinal traction. *Br J Ophthalmol*. 2012;96(3):356-359. doi:10.1136/bjophthalmol-2011-300141
9. Lin CJ, Hwang JF, Chen YT, Chen SN. The effect of intravitreal bevacizumab in the treatment of coats disease in children. *Retina*. 2010;30(4):617-622. doi:10.1097/IAE.0b013e3181c2e0b7
10. Yang Q, Wei W, Shi X, Yang L. Successful use of intravitreal ranibizumab injection and combined treatment in the management of Coats' disease. *Acta Ophthalmol*. 2016;94(4):401-406. doi:10.1111/aos.13067
11. Zheng XX, Jiang YR. The effect of intravitreal bevacizumab injection as the initial treatment for Coats'

disease. *Graefe's Arch Clin Exp Ophthalmol*. 2014;252(1):35-42. doi:10.1007/s00417-013-2409-1

12. Li S, Deng G, Liu J, Ma Y, Lu H. The effects of a treatment combination of anti-VEGF injections, laser coagulation and cryotherapy on patients with type 3 Coat's disease. *BMC Ophthalmol*. 2017;17(1):1-7. doi:10.1186/s12886-017-0469-4
13. Shapiro MJ, Chow CC, Karth PA, Kiernan DF, Blair MP. Effects of green diode laser in the treatment of pediatric coats disease. *Am J Ophthalmol*. 2011;151(4):725-731.e2. doi:10.1016/j.ajo.2010.10.024
14. Mulvihill A, Morris B. A population-based study of Coats disease in the United Kingdom II: Investigation, treatment, and outcomes. *Eye*. 2010;24(12):1802-1807. doi:10.1038/eye.2010.127
15. Levinson JD, Hubbard GB. 577-NM yellow laser photocoagulation for coats disease. *Retina*. 2016;36(7):1388-1394. doi:10.1097/IAE.0000000000000874
16. Grosso A, Pellegrini M, Cereda MG, Panico C, Staurenghi G, Sigler EJ. Pearls and pitfalls in diagnosis and management of coats disease. *Retina*. 2015;35(4):614-623. doi:10.1097/IAE.0000000000000485
17. Böhm MRR, Uhlig CE. Use of intravitreal triamcinolone and bevacizumab in Coats' disease with central macular edema. *Graefe's Arch Clin Exp Ophthalmol*. 2011;249(7):1099-1101. doi:10.1007/s00417-011-1629-5
18. He YG, Wang H, Zhao B, Lee J, Bahl D, McCluskey J. Elevated vascular endothelial growth factor level in Coats' disease and possible therapeutic role of bevacizumab. *Graefe's Arch Clin Exp Ophthalmol*. 2010;248(10):1519-1521. doi:10.1007/s00417-010-1366-1
19. Cebeci Z, Bayraktar Ş, Yılmaz YC, Tuncer S, Kır N. Evaluation of follow-up and treatment results in coats' disease. *Turk Oftalmoloiji Derg*. 2016;46(5):226-231. doi:10.4274/tjo.12754
20. Arevalo JF, Maia M, Flynn HW, et al. Tractional retinal detachment following intravitreal bevacizumab (Avastin) in patients with severe proliferative diabetic retinopathy. *Br J Ophthalmol*. 2008;92(2):213-216. doi:10.1136/bjo.2007.127142
21. Villegas VM, Gold AS, Berrocal AM, Murray TG. Advanced Coats' disease treated with intravitreal bevacizumab combined with laser vascular ablation. *Clin Ophthalmol*. 2014;8:973-976. doi:10.2147/OPTH.S62816
22. Zhang L, Ke Y, Wang W, Shi X, Hei K, Li X. The efficacy of conbercept or ranibizumab intravitreal injection combined with laser therapy for Coats' disease. *Graefe's Arch Clin Exp Ophthalmol*. 2018;256(7):1339-1346. doi:10.1007/s00417-018-3949-1

Table 1. Characteristics of the studies

No	Author	Year	Level of evidence	Time frame	Subject (eye)	Staging of Coats (pre-treatment)	Mean Age	Treatment	Dose	Follow-Up Period
		Comparative Study								
1	Ray R, et al[1]	2012	IV (Case series)	1 January 2001-31 March 2010	10 eyes/group	Group 1: ranging from 2B-3B Group 2: ranging from 2B-3B	4.88 years (group 1) and 4.64 years (group 2)	Group 1: intravitreal **bevacizumab** combined with laser or cryotherapy Group 2: ablative therapy (laser and/or cryotherapy)	0.625 mg or 1.25 mg of bevacizumab injection **1 – 3 times**	10-19.6 months (group 1) 10.1-138.9 months (group 2)
		Main therapy: anti-vascular endothelial growth factor (anti-VEGF) injection								
2	Lin CJ, et al.[9]	2010	IV (Case series)	2005-2008	3 eyes	Case A: stage 2B Case B: stage 3B Case C: stage 3A	5.5 years (A: 10 years old; B: 6 month old; C:12 years old)	Only intravitreal **bevacizumab** injection (primary treatment) Ablative procedures after subretinal fluid completely resolved	2.5 mg/0.1 mL, 1 – 3 times **Mean: 2.33 times**	1 year (12 months)
3	Li S, et al.[12]	2017	IV (retrospective non-controlled clinical sdtudy)	April 2013-September 2016	17 eyes	stage 3A (n=10) stage 3B (n=7)	4.94 ± 2.92 years	Intravitreal **ranibizumab** injection (initial treatment), subsequent cryotherapy and laser photocoagulation depended on the absorption of subretinal fluid)	0.05 mL (10 mg/mL) 1 – 5 times **Mean: 2.82 ± 0.95 times**	18 – 35 months (range) 24.12 ± 5.99 months (mean)
4	Yang Q, et al.[10]	2016	III (prospective non-controlled clinical trial)	January 2014 – February 2015	17 eyes	stage 3A (n=6) stage 3B (n=11)	7.9±3.8 years	Intravitreal **ranibizumab** injection monthly for the first 3 months Retreatment regimen given at **any time** during follow-up period	0.5 mg/0.05 mL 3 – 6 times **Mean: 3.9 ± 1.0 times**	3 – 16 months (range) 9.7 ± 3.3 months (mean)
5	Rama-subrama-nian A, et al[8]	2011	IV (retrospective review)	August 2007-February 2009	8 eyes	stage 2 (n=1) stage 3A (n=3) stage 3B (n=4)	88 months	Intravitreal **bevacizumab** injection according to clinical response Subsequent cryotherapy (n=8), laser photocoagulation (n=4), subTenon's fascia triamcinolone (12% of pts)	0.05 mL (1.25 mg) 1 – 4 times **Mean: 1 injection per eye**	8.5 months (mean)

6	Zheng XX, et al[11]	2010	IV (retrospective review)	April 2010 – May 2012	14 eyes	stage 2 (n=1) stage 3A (n=9) stage 3B (n=4)	6.9 years (range 4-11 years)	Novel initial treatment of intraocular **bevacizumab** laser, cryotherapy as needed during follow-up period	0.05 mL (1.25 mg) 1 – 5 injections **Mean: 2.9 injections**	6 – 24 weeks
	Main therapy: standard/focal therapy									
7	Shapiro MJ, et al.[13]	2011	IV (retrospective interventional case series)	September 2002 – May 2008	14 eyes	stage 2 and stage 4 (n=1) stage 3 (n=12)	57 months (range 0.5 – 153 months)	Green diode laser ablation therapy (532-nanometer green diode) using 28- and 20-diopter lenses	Duration: 1000 ms; console settings: 200 – 1000 mW	Mean: 41 months Range: 15-70 months
8	Levinson JD, et al.[15]	2016	IV (retrospective consecutive case series)	December 2011 – December 2014	17 eyes	stage 1 (n=1), stage 2A (n=2), stage 2B (n=6), stage 3A (n=3), stage 3B (n=5)	71.2 months	577-nm yellow wavelength LIO, without bevacizumab / cryotherapy	Power: 150 – 300 mW	Mean: 20.8 months Range: 3.7 – 37.3 months
9	Mul-vihill A, et al.[14]	2010	III (prospective population based study)	January 2008 – January 2009	55 eyes	Stage 2A (n=10), stage 2B (n=17), stage 3A (n=11), stage 3B (n=3)	168 months	Argon laser, FD-YAG laser, diode laser, cryotherapy, argon + cryo Adjuvant: intravitreal anti-VEGF adjunctive therapy	Not mentioned	6-month follow up

Table 2. Anatomical outcomes in included studies

Studies	Retinal detachment	Telangiectasia quadrants	Resolution of exudates
Comparative Study			
Ray R, et al.[1]	Group A: SRF in 1.7 quadrants Group B: SRF in 1.2 quadrants	Group A: 2.4 quadrants Group B: 2.2 quadrants	Not mentioned
Main therapy: anti-VEGF injection			
Lin CJ, et al.[9]	Case 1: resolved Case 2: resolved Case 3: resolved	Not mentioned	Case 1: resolved Case 2: resolved Case 3: not recurrent
Li S, et al.[12]	Pre-treatment RD height measured by OCT: 2363.88 µm Post-treatment: 897.18 µm (p = 0.000)	Not mentioned	Not mentioned
Ramasubra-manian A, et al.[8]	Significant resolution: 50% (n=4) Partial: 50% (n=4) Non-regression: 0% (n=0)	Significant: 62% (n=5) Partial: 38% (n=3) Non-regression: 0% (n=0)	Significant: 75% (n=6) Partial: 25% (n=2) Non-regression: 0% (n=0)
Yang Q, et al.[10]	Completely reattached: 23.5% (n=4) Partially reattached: 58.8% (n=10) Aggravated retinal detachment: 5.9% (n=1)	Regression: 100% (n=17)	Resolution of exudation: 47.1% (n=1) Aggravated of exudation: 5.9% (n=1)
Zheng XX, et al.[11]	Resolution of SRF: 100% (n=14)	Regression: 100% (n=14)	Resolution of exudation: 100% (n=14)
Laser / focal treatment			
Shapiro MJ, et al.[13]	Resolution of SRF: 92.8% (n=13)	Not mentioned	Resolution of exudation: 100% (n=14)
Mulvihill A, et al.[14]	Not mentioned	Not mentioned	Not mentioned
Levinson JD, et al.[15]	Resolution of SRF: 94.1% (n=16)	Not mentioned	Not mentioned

Table 3. Reported complications in included studies

Studies	Vitreoretinal fibrosis	Tractional retinal detachment	Other complications	Note
Combined Anti-VEGF + laser therapy				
Ramasubramanian A, et al.[8]	50% of subjects (n=4)	38% of subjects (n=3)	N/A	P *value* not stated
Zheng XX, et al.[11]	Subretinal fibrosis: 0% Epiretinal fibrosis: 7.1% (n=1)	N/A	N/A	P *value* not stated
Focal therapy (laser photocoagulation)				
Levinson JD, et al.[15]	Subretinal fibrosis: 5.9% (n=1)	5.9% of subjects (n=1)	Cataract: 11.8% of subjects (n=2) Vitreous hemorrhage: 11.8% of subjects (n=2)	P *value* not stated