Diploma Thesis

Treatment of myopic choroidal neovascularization: a network meta-analysis and review

Submitted by

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in partial fulfillment of the requirements for the degree of

Doktorin der gesamten Heilkunde

(Dr.in med.univ.)

at the

Medical University of Graz

executed at the

University Clinic for Ophthalmology

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Graz, 10.02.2023

Declaration of Academic Integrity

I herewith declare that I have composed the present diploma thesis independently without any further assistance. The present thesis is the result of my independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material was used other than the declared sources and aids provided in the reference list. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 10.02.2023 Glachs Laura eh

Acknowledgements

At this point I would like to express my sincere thanks to Univ.-Prof. Dr.med.univ. Wedrich Andreas and Dr.in med.univ. Posch-Pertl Laura for their extraordinary commitment and great support. Many thanks for the motivation and encouragement during the network meta-analysis, study and whole thesis!

Furthermore, I would like to thank the Institute for Medical Data Processing, Statistics and Documentation, in particular the director Univ.-Prof.in Dipl.-Ing.in Dr.intechn. Berghold Andrea and of course Dipl.-Ing. Embacher Stefan. Thank you for your support, tireless efforts and accurate statistical analysis. I would also like to thank Mag.a Wildner Brigitte for the complex literature research.

My special thanks go to my family and friends, particularly to my mum Isolde Glachs and aunt Jasmin Doba, who both supported and encouraged me unconditionally at all times.

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List of Abbreviations

A.= arteria

Aa. = arteriae

AEs = adverse events

AL = axial length

AMD = age-related macular degeneration

Anti-VEGF = anti vascular endothelial growth factor

BCVA = best corrected visual acuity

CNV = choroidal neovascularization

CRT = central retinal thickness

DR = diabetic retinopathy

EDTRS = Early Treatment Diabetic Retinopathy Study

FA/FLA = fluorescein angiography

FAZ = foveal avascular zone

FU = follow-up

IOL = intraocular lens

IOP = intraocular pressure

IVB = intravitreal bevacizumab

IVR = intravitreal ranibizumab

N/d = not defined

N = number of eyes

nAMD = neovascular age-related macular degeneration

OCT = optical coherence tomography

PDT = photodynamic therapy

PM = pathologic myopia

PRN = pro re nata

PRP = panretinal photocoagulation

RPE = retinal pigment epithelium

RVO = retinal vein occlusion

SAEs = severe adverse events

TCA = triamcinolone

VA = visual acuity

VEGF = vascular endothelial growth factor

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Zusammenfassung

Ziel

Die Behandlungsoptionen der myopen choroidalen Neovaskularisation (CNV) umfassen die Verteporfin-Photodynamische Therapie (PDT), chirurgische Eingriffe, intravitreal appliziertes Triamcinolon (TCA) sowie „anti–vascular endothelial growth factor“ (Anti-VEGF). Bisher wurde keine Netzwerk Metaanalyse durchgeführt, in der die Wirksamkeit der Behandlungsstrategien verglichen wurden.

Methoden

Elektronische Datenbanken wurden nach verschiedenen Therapieoptionen und der myopen CNV von Datenbankgründung bis 7/2020 durchsucht. Titel, Abstracts sowie Volltexte wurden von zwei unabhängigen Gutachterinnen bewertet und die Ergebnisse der Studien zusammengefasst und analysiert. Die Wirksamkeit der Therapieoptionen wurde durch zwei primäre Endpunkte bestimmt: Verbesserung der bestkorrigierten Sehschärfe (BCVA) in Buchstaben und anatomische Veränderungen der zentralen Netzhautdicke (CRT) in Mikrometern. Ergebnisse wurden in eine Frühphase (≤6 Monate) und eine Spätphase (>6 Monate) unterteilt. Eine Subgruppenanalyse der verschiedenen Anti-VEGF-Präparate, ihrer Behandlungsschemata und Anzahl der Injektionen wurde durchgeführt.

Ergebnisse

Vierunddreißig Studien (2.016 Augen) wurden in die quantitative Netzwerk Metaanalyse eingeschlossen. In der Frühphase führte der Einsatz von Anti-VEGF zu einem Anstieg von 14.1 Buchstaben (95 % CI, 10.8-17.4; p<0.0001) im Vergleich zur unbehandelten Gruppe, von 12.1 (95 % CI, 8.3-15.9; p<0.0001) zu PDT und von 7.5 (95 % CI, 1.2-13.8; p=0.019) zu TCA. In der Spätphase verhielt es sich ähnlich. Anti-VEGF führte in der Frühphase zu einer größeren Abnahme der CRT im Vergleich zur unbehandelten Gruppe (66.8 µm; 95 % CI, 40.2-93.4; p<0.0001) und im Vergleich zu PDT (27.7 µm; 95 % CI, 16.1-39.3; p<0.0001). Die Kombination PDT + Anti-VEGF zeigte einen größeren Rückgang der CRT gegenüber Anti-VEGF (12.0 µm; 95 % CI, 21.4-2.6; p=0.013).

Die Anti-VEGF-Präparate schnitten bei beiden Endpunkten ähnlich ab. Einzig bei der Abnahme der CRT zeigte sich unter Aflibercept ein stärkerer Rückgang im Vergleich zu Bevacizumab (12.1 µm; 95 % CI, 3.0-21.2; p=0.009; ≤6 Monate).

Beim Vergleich der Behandlungsstrategie, gab es keinen Unterschied zwischen einer initialen Dosis (1+pro re nata (PRN)) und drei initialen Dosen (3+PRN). Allerdings erhielt die 1+PRN-Gruppe 1.8 (SD 1.3), die 3+PRN-Gruppe hingegen 3.2 (SD 0.9) Injektionen innerhalb von zwölf Monaten ($p<0.0001$).

Schlussfolgerung

Diese Netzwerk Metaanalyse bekräftigt die Anti-VEGF-Behandlung als Erstlinientherapie der myopen CNV. Die Anti-VEGF-Präparate erscheinen gleichermaßen wirksam. Das 1+PRN-Schema erscheint sinnvoll, um die Anzahl an Injektionen gering zu halten.

Abstract

Purpose

Treatment options of myopic choroidal neovascularization (CNV) include verteporfin-photodynamic therapy (PDT), surgical treatment, intravitreal triamcinolone (TCA) and anti-vascular endothelial growth factor (anti-VEGF). A network meta-analysis, comparing different treatments has not been carried out yet.

Methods

Electronic databases and the Web of Science were searched for different therapies and myopic CNV from database inception to 7/*2020*. Retrieved titles, abstracts, full-texts and their results were summarized by two independent reviewers. Treatment's efficacy was determined by two primary endpoints: improvement in best-corrected visual acuity (BCVA) in letters and anatomical changes in central retinal thickness (CRT) in micrometers. Results were divided into early (≤6 months) and late phase (>6 months). Subgroup analyses of different anti-VEGF agents, their treatment regimen and injection number were performed.

Results

Thirty-four studies (2.016 eyes) were included in the quantitative network meta-analysis. In the early phase, the use of anti-VEGF resulted in an increase of 14.1 letters (95 % CI, 10.8-17.4; p<0.0001) compared to untreated, of 12.1 (95 % CI, 8.3-15.9; p<0.0001) to PDT and of 7.5 (95 % CI, 1.2-13.8; p=0.019) to TCA. In the later phase, these results were largely maintained. In the early phase, anti-VEGF led to a decrease in CRT in comparison to untreated (66.8 µm; 95 % CI, 40.2-93.4; p<0.0001) and to PDT (27.7 µm; 95 % CI, 16.1–39.3; p<0.0001). Combination of PDT and anti-VEGF resulted in a greater decrease in CRT compared to anti-VEGF alone (12.0 µm; 95 % CI, 21.4-2.6; p=0.013).

The different VEGF inhibitors showed similar results, except that aflibercept showed a greater decrease in CRT compared to bevacizumab (12.1 µm; 95 % CI, 3.0-21.2; p=0.009; ≤6 months).

There were no significant differences whether anti-VEGF was applicated as one initial (1+pro re nata (PRN)) or three initial doses (3+PRN). However, the 1+PRN

group received 1.8 (SD 1.3) injections, while the 3+PRN received 3.2 (SD 0.9) within twelve months ($p<0.0001$).

Conclusion

This network meta-analysis confirms that the first-line therapy for myopic CNV are VEGF inhibitors. Different anti-VEGF drugs appear equally effective. 1+PRN regimen seems reasonable to keep the injection number low.

1 Introduction

1.1 The Eye

The eye itself consists of several anatomical structures, each of which performs its own tasks. To enable the complex functionality of this sensory organ there is the eye, the appendage organs and the visual pathway (1).

1.1.1 Eyeball (Bulbus oculi)

The mayor part of the eyeball is composed of three layers. These are from the outside to the inside the sclera, uvea and retina (1, 2).

However, the anterior part of the eyeball deviates from this construction. There, the outer layer of the eyeball is formed by the cornea. At the limbus corneae, it merges into the less curved sclera. The sclera and the cornea form the tunica fibrosa bulbi. All external eye muscles attach to this coarse connective tissue. In the anterior part of the eye the sclera forms the trabecular meshwork located in the chamber angle. At the back the sclera forms the lamina cribrosa, through which the axons of the optic nerve exit (1, 2).

Below the sclera lies the vascular membrane (tunica vasculosa bulbi or uvea). It consists of three sections: iris, ciliary body (corpus ciliare) and choroidea, with the choroidea extending around the posterior eyeball. The iris shields the eye from excessive light and covers the lens. Its root merges into the ciliary body, which contains the ciliary muscle that is responsible for accommodation. At the ora serrate the ciliary body merges into the choroidea, the posterior and largest part of the middle layer of the bulbus (1, 2).

The innermost layer of the eyeball, the retina (tunica interna bulbi), contains the light-sensitive sensory cells (retina) and the pigment epithelium. The approximately 4 mm macula with the fovea centralis represents the site of sharpest vision. Incident light is normally focused on it (1, 2).

The eyeball is filled by the vitreous body (corpus vitreum). The vitreous stabilizes the bulbus. It consists of 98 % water and 2 % hyaluronic acid and collagen and does not contain nerves and vessels (1, 2).

1.1.2 Refractive media

There are four refractive media located in the eye: the cornea, the lens, the vitreous body and the aqueous humor. They focus light onto the retina. The cornea has the highest refractive power (about 43 diopters). The cornea is avascular and receives oxygen and nutrients through the tear film and the aqueous humor. The clear and 4 mm thick lens lies between the iris and the vitreous body. It is connected to the ciliary muscle by very fine fibers (zonula fibers), whose contraction changes the shape and length of the lens. The lens contains neither nerves nor vessels. The lens is biconvex and curved more posteriorly than anteriorly. It is used for fine adjustment of light rays and has a refractive power of 10-20 diopters depending on the accommodation condition (1, 2).

The degree of curvature of the lens is regulated by the muscles of the circular ciliary body. If the distance between an object and the eye is less than 5 m, the lens becomes more spherical to fixate the object. This can be accomplished by the contraction of the ciliary muscle (parasympathetic innervation from the oculomotoric nerve), which causes the zonular fibers to relax and the lens to assume its more convex relaxed shape due to its inherent elasticity. This mechanism is the basis of accommodation. When the eye adjusts for distant vision, the ciliary muscle relaxes, which causes the zonular fibers to pull and the lens to flatten (1, 2).

1.1.3 Iris

The iris, together with the choroid and the ciliary body, into which its outer edge merges, is part of the vascular skin (uvea). The pigments that determine eye color are formed in it. The iris forms a pinhole in front of the lens with a central opening, the pupil. The aperture (diameter 1-8 mm) narrows on contraction of the sphincter pupil muscle (parasympathetically innervated by the oculomotor nerve) and dilates on contraction of the dilator pupil muscle (sympathetically innervated via the internal carotid plexus) (1, 2).

The pupil width is normally regulated by the incidence of light and serves primarily to improve image sharpness. In healthy individuals, the pupils are circular and of

equal size (normal width 3-5 mm). Due to different influences (light, medication, disease) the pupil width can vary between 8 mm (= mydriasis) and 1.5 mm (= miosis) (1, 2).

1.1.3.1 Anterior and posterior chamber

Iris and lens separate the anterior and posterior eye chambers in which aqueous humor is located. This fluid (about 0.3 ml per eye) primarily determines the internal pressure of the eye. It is produced by the non-pigmented ciliary epithelium of the ciliary processes in the area of the posterior chamber of the eye (about 0.15 ml/h) and enters the anterior chamber of the eye through the pupil. Via the clefts of the trabecular meshwork in the area of the chamber angle the aqueous humor seeps into the canal of Schlemm (sinus venosus sclerae), from there further into the episcleral veins. The outflowing aqueous humor flows due to a pressure gradient in the direction of the chamber angle and has to overcome two physiological resistances (the papillary resistance between iris and lens and the trabecular resistance). Approximately 85 % of the aqueous humor flows via the trabecular meshwork into the canal of Schlemm, the remaining 15 % enter the vortex veins via the uveoscleral vascular system (1, 2).

Normal adult intraocular pressure (10-21 mmHg) is required for a functioning optical system causing a smooth curvature of the corneal surface as well as pressing the photoreceptor cells against the pigment epithelium. In glaucoma, this pressure is increased so that the optic nerve is damaged. The most common glaucoma type is the open-angle glaucoma, in which the drainage site remains open (1, 2).

1.1.4 Retina

The retina is the innermost layer of the eyeball. It consists mainly of a light-sensitive part, the pars optica retinae, and to a smaller extent of a light-insensitive part, the pars caeca retinae. The place of the sharpest vision on the retina is the retinal pit (fovea centralis retinae), a small depression in the center of the yellow spot (macula lutea) (1, 2).

The retina consists of ten layers. Before the light reaches the light-sensitive parts of the photoreceptors, it must pass through all the layers that lie on the inside (inversion of the retina). The action potentials, on the other hand, run in the opposite direction

of light from the outside to the inside. The first three projection neurons of the visual pathway are located within the retina (1, 2).

First neuron: Photoreceptor cells are light-sensitive sensory cells that convert light stimuli into electrochemical signals. There are two types of photoreceptors, the rods and cones. There are 100-125 million rods responsible for twilight and night vision, but only 6-7 million cones responsible for red, green and blue perception (1, 2).

Second neuron: Bipolar cells receive signals from the photoreceptors and transmit them to the ganglion cells (1, 2).

Third neuron: Ganglion cells whose neurites unite at the papilla to form the optic nerve and travel toward the corpus geniculatum laterale (to the fourth neuron) (1, 2).

Since the optic nerve is an outpouching of the diencephalon, it is surrounded, by all the meninges (dura mater, arachnoid mater and pia mater) as well as subarachnoid space filled with cerebrospinal fluid, which communicates with the cerebrospinal fluid of the brain and spinal cord (1, 2).

In addition, there are horizontal cells and so-called amacrine cells, which build lateral connections in the retina. They are mainly responsible for lateral inhibition, which is important for several visual functions (1, 2).

The macula lutea is located temporal to the papilla of the optic nerve. In its center lies a funnel-shaped depression, the fovea centralis, which is the site of sharpest vision (diameter approximately 1.5 mm). There, the inner retinal layers are displaced to the edge of the funnel, so that the cells of the photoreceptors are directly exposed to the incident light (1, 2).

1.1.5 Blood supply

The arteries of the eyeball all originate from the ophthalmic artery, an end branch of the internal carotid artery. It gives off several branches to supply the eye:

The a. (arteria) centralis retinae to the retina, the aa. (arteriae) ciliares posteriores breves to the choroidea, the aa. ciliares posteriores longae to the ciliary body and iris, where they supply the two vascular rings (circulus arteriosus iridis minor and major) as well as the aa. ciliares anteriores, which originate from vessels of the straight eye muscles and anastomose with the posterior ciliary vessels (1, 2).

1.1.6 Eye movement

Eye movements are controlled by the six external eye muscles. The lateral rectus muscle, which is the only muscle innervated by the abducens nerve (VI), responsible for the abduction. The medial rectus muscle, innervated by the oculomotoric nerve (III), responsible for adduction. The inferior rectus muscle, also innervated by the oculomotoric nerve (III), responsible for depression of the bulb as well as external rotation and adduction. The superior rectus muscle, innervated by the oculomotoric nerve (III), responsible for elevation as well as internal rotation and adduction. The obliquus inferior muscle, innervated by the oculomotoric nerve (III), responsible for external rotation as well as elevation and abduction. The superior oblique muscle, solely innervated by the trochlear nerve (IV), responsible for internal rotation as well as depression and abduction (1, 2).

1.2 Refractive Errors

1.2.1 The emmetropic eye

If the eye has a spherical equivalent of less than 0.50 diopters and a maximum astigmatism of 0.75 diopters, it is an emmetropic eye (3). The refraction of parallel rays from infinity (distance vision) are refracted by the cornea and lens placing the focus point directly on the retina (2).

1.2.2 Myopia

In myopic eyes distant objects are perceived out of focus. Light rays entering parallel to the optical axis are focused in front of the retina instead of directly on the retina. The reason could be a too long eyeball (axial myopia) or a too strongly curved cornea and/or lens with increased refractive power (refractive myopia). Myopia can also be caused by a specific condition such as drugs or a clinical syndromes, referred to as secondary myopia (4, 5).

If the spherical equivalent with relaxed accommodation of the eye is ≤-0.5 diopters, it is called myopia. In low myopia, the spherical equivalent refractive error of an eye lies between -0.50 and -6.00 diopters. In high myopia, the spherical equivalent refractive error is ≤-6.00 diopters (4, 5).

1.2.3 Hyperopia

Parallel rays from infinity are bundled behind the retina, caused by a too short eyeball (axial hyperopia) or too weak refractive media caused by a too flat cornea, lens or both, (curvature hyperopia) when accommodation is at rest. Nearby objects occur blurred. The spherical equivalent must be ≥+0.5 diopters (2, 3, 5).

1.2.4 Presbyopia

With increasing age, the eye loses the ability to provide efficient accommodation. This is a result of the increasing stiffness as well as thickness of the lens. Therefore, the shape, refractive power and focus cannot be changed when the ciliary muscle contracts making the near sight impossible (5).

1.3 Pathologic Myopia

1.3.1 Definition

When excessive axial elongation of the eyeball, which can lead to myopia as mentioned above, occurs in combination with structural changes in the posterior segment of the eye, it is termed pathologic myopia. “Pathologic myopia” is not the same as “high myopia”. High myopia is characterized as a high degree of myopic refractive error while “pathologic myopia” has typical myopic lesions. The typical changes for pathologic myopia include posterior staphyloma, myopic maculopathy and optic neuropathy as well as loss of best corrected visual acuity (BCVA) (4). No limits for refractive error and axial length were set to define and standardized pathologic myopia. One reason is, that posterior staphyloma can occur even with normal axial lengths (6) or even with axial lengths less than 26.5 mm (7). So, there are still several differing definitions of pathologic myopia. Nevertheless, the most common definition comprises a refractive error of less than -6.00 diopters, an axial length of ≥26.5 mm and degenerative lesions of either the sclera, choroid, or retina (8-10).

1.3.2 Prevalence

Pathologic myopia affects nearly 2 % of the general population. Due to its complications, it is one of the most frequent causes of blindness worldwide (11-14). In recent years, the prevalence of myopia and high myopia has increased rapidly because of environmental and lifestyle factors. This could lead to an increase in the prevalence of pathologic myopia. Since, the development of pathologic myopia is associated with the occurrence of high myopia even though pathologic myopia may also occur in emmetropic eyes (15).

1.3.3 Complications

One of the most serious and frequent complications affecting central vision or even leading to complete blindness is choroidal neovascularization (CNV) (11). CNV is an abnormal growth of blood vessels from the choroid through the Bruch’s membrane, eventually causing leakage and hemorrhage leading to loss of vision. CNV can develop in many entities such as myopia and age-related macular degeneration (16). In untreated patients, the central vision can deteriorate rapidly. Within eight years, more than one-third of patients develop a myopic CNV in the second eye (17).

1.4 Rationale of the study

Although pathologic myopia with its serious consequential diseases especially CNV affects a high proportion of the population, the verteporfin-photodynamic therapy (PDT) was the only treatment approved to treat myopic CNV, for a long time (8, 18, 19). This treatment modality could stabilize the disease progression in the short-term but did not show positive results in the long-term (19-21). Surgical interventions led to a temporary improvement only and involved high complication rates (22, 23). The introduction of anti-vascular endothelial growth factors (anti-VEGF) as new treatment option led to a therapeutic revolution. This innovative therapy soon replaced PDT as the new gold standard in the treatment of myopic CNV (20, 24-27).

In the past, several studies (19, 27-43) have been conducted to compare all different treatment modalities. The key deficiency is, that a common comparator has not been used yet. Therefore, a study was conducted in the course of this thesis to compare the efficacy of different treatment options for myopic CNV using a network meta-analysis.

2 Material und Methods

2.1 Ethic votum

An ethical vote was not required, as the data used was taken from the retrieved studies, which have already anonymized their results.

2.2 Literature search

In collaboration with an experienced medical informatician (Mag.ª Wildner Brigitte) from the University of Vienna, the literature search was performed. Electronic databases, more precisely MEDLINE, Embase, Cochrane Central Register of Controlled Trials and Web of Science (SCI-Expanded, SSCI, CPCP-S and ESCI), were searched from database inception to *July 2020.* Both controlled term as well as free term formulations were used. The following keywords were utilized to identify the studies of interest: “myopic choroidal neovascularization” AND “treatment”; - AND “aflibercept”; - AND “bevacizumab”; - AND “ranibizumab”; - AND “conbercept”; - AND “PDT”; - AND “photodynamic therapy”; - AND “triamcinolone”; - AND “sham”. Thereafter, only English-published articles were taken into consideration. To survey overlooked manuscripts so far, the bibliographies of the identified articles were scanned to find additional potentially suitable manuscripts. No registration of the protocol of this network meta-analysis has been made in PROSPERO. This review was performed using the Cochrane Handbook and the PRISMA checklist for network meta-analyses (see Figure 1 and Supplementary Table 3) (44, 45).

2.3 Study eligibility criteria

Randomized controlled, prospective and retrospective cohort studies, cross-sectional studies, case-control studies, surveys and surveillance reports comparing different treatment modalities were included in the analysis. In addition, studies had to meet several criteria for being included: at least two treatment groups, original data from adult patients (≥18 years), a sample size of ≥10 and English as publication language. Abstracts and conference proceedings not published in peer-reviewed journals were not considered.

2.4 Study selection

In the context of this thesis two reviewers (the thesis supervisor Dr.in med.univ. Posch-Pertl Laura and cand.med. Glachs Laura) verified suitable references. Afterwards, the identified titles were submitted to an abstract and subsequent full text review to finally decide whether they met the required conditions and could be included. Disagreements were clarified through discussion. To assist the verification process of screening abstracts and full texts, the software “Rayyan” (46, 47) was used.

2.5 Data extraction

The same two investigators defined the data of importance and extracted it independently. The data included more precisely: title, name of authors, year of publication, study design, sample size, treatment, BCVA at baseline and follow-up, central retinal thickness (CRT) at baseline and follow-up, number of treatments and demographic data. In order to enable the comparison of the BCVA, the different reporting styles were converted to the letters scale. Also, descriptive data including country of origin, definition of myopic CNV, minimal axial length, inclusion and exclusion criteria and pretreatment was recorded. A Microsoft Excel (Microsoft Cooperation) spreadsheet was used to manage and organize the data.

2.6 Data Analysis

The data analysis was performed by a faculty member (Dipl.-Ing. Embacher Stefan) of the Institute for Medical Informatics, Statistics and Documentation (Medical University of Graz).

The efficacy of each treatment was determined by two outcome variables: the visual acuity improvement measured by the BCVA in letters and the anatomical recovery measured by the CRT in micrometers. The variables (change in BCVA and CRT of each treatment group) were calculated by the mean-difference between baseline and follow-up. A high percentage of studies reported means and standard deviations at baseline and for specific follow-up dates.

The Cochrane Handbook for Systematic Reviews of Interventions (48) was followed to calculate the standard deviation of change, assuming a correlation of 0.6 between baseline and follow-up values. A Methods Research Report (49) found a median of

0.59 for correlation between baseline and follow-up. In one of the included studies a correlation of 0.646 was provided (50). As a sensitivity analysis, no correlation was assumed. In case of missing values, further measures were taken to calculate change and the corresponding standard deviation of the visual results. Therefore, p-values and confidence intervals were utilized and as a last option, if the standard deviation for the follow-up date was missing but the standard deviation for the baseline value was given, the baseline value was used as a surrogate.

Correlations in multi-arm studies were considered and the network meta-analysis was based on a random effects model (51). A generalized DerSimonian-Laird estimator was used to estimate the common heterogeneity variance τ^2 needed for the random effects model (52). To assess inconsistency, the between-designs Q statistic was calculated based on a full design-by-treatment interaction random effects model (53).

The efficacy of the different treatments for two different time points and two separate outcomes was compared. The follow-up data was divided into two groups, the first to describe treatment in the earlier phase from one to six months. In case of multiple follow-up data, priority was given to three months, then to six months and as a last option to one month. The second group represents the later phase, in which data was prioritized in the following order: twenty-four months, then twelve months, and as the last option, all follow-up appointments after twenty-four months.

Furthermore, the different anti-VEGF agents were analyzed separately, comparing the same time points and outcomes. The analysis did not differentiate between a single initial injection followed by a pro re nata approach (1+PRN) and three initial injections followed by a PRN approach (3+PRN). A pairwise meta-analysis to evaluate possible differences between the two treatment regimens was carried out individually. Also, the number of treatments were compared using a two-sample t-test with Welch-Satterthwaite correction on pooled standard deviations and means. In all analyses a p-value of less than 0.05 was considered statistically significant and were performed in R, Version 4.1.3 (54).

3 Results

3.1 General characteristics

The literature search found 1.446 articles (see Figure 1). 165 full text articles of these were reviewed for eligibility. In the end sixty-three studies were included in the qualitative and thirty-four studies in the quantitative analysis (see Supplementary Table 1 and 2).

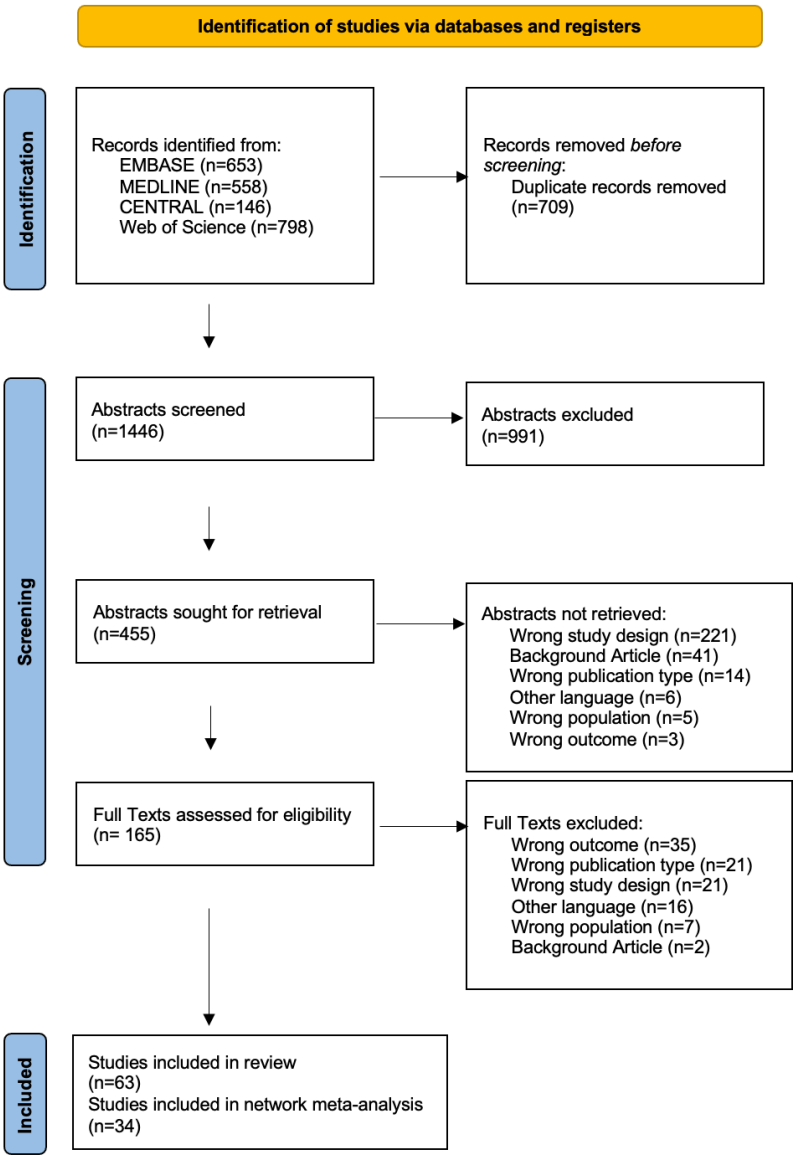

Figure 1: PRISMA Flow Diagram adapted by Page et al. (44) © Dr.in med.univ. Posch-Pertl Laura

3.2 Study characteristics

The thirty-four studies that were quantitatively analyzed included 2.016 eyes from 1.971 patients, consisting of twenty-nine two-arm and five three-arm studies. The sixty-three studies, precisely 4.615 eyes, analyzed qualitatively comprise fifty-one two-arm studies, ten three-arm studies, one four-arm study and one five-arm study.

3.3 Outcome in the earlier phase (≤6 months)

In the earlier phase, ten studies representing six different arms were analyzed regarding BCVA. The evidence network depicts this analysis graphically (see Figure 2). The numbers represent the quantity of direct comparisons, while the thickness of the lines is proportional to the inverse standard error of the estimates.

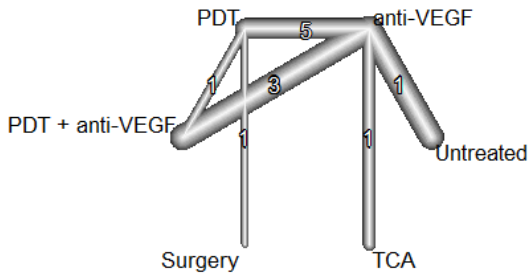

Figure 2: Network graph comparing the structure of the network regarding different treatments based on BCVA in the early phase (≤6 months). © Dipl.-Ing. Embacher Stefan

A favorable outcome using anti-VEGF treatment compared to untreated patients was shown. Patients treated with anti-VEGF had a mean estimated gain of 14.1 letters (95 % CI, 10.8-17.4; p<0.0001) compared to untreated patients. In comparison to PDT a mean estimated gain of 12.1 letters (95 % CI, 8.3-15.9; p<0.0001) and to triamcinolone (TCA) of 7.5 letters (95 % CI, 1.2-13.8; p=0.019) was obtained in patients treated with anti-VEGF. In contrast, no significant difference between anti-VEGF treatment and the combination of PDT and anti-VEGF treatment was recorded (-2.9; 95 % CI, -6.0–0.2; p=0.065). The TCA treatment group accounted a mean difference of 6.6 letters (95 % CI, -0.5-13.7; p=0.068) compared to untreated patients. The PDT treatment group failed to surpass the untreated group with a difference in letters amounting -2.01 (95 % CI, -7.0-3.0; p=0.430). The mean difference in letters of 5.9 (95 % CI, −5.0-16.8; p=0.288) of the surgical group compared to the anti-VEGF group stayed statistical insignificant (see Figure 3). Furthermore, the network did not show evidence of inconsistency (p=0.204).

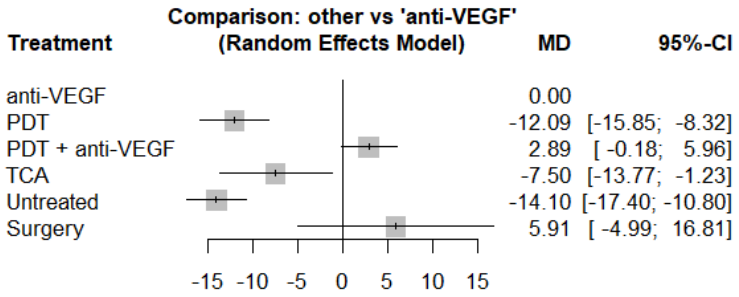

Figure 3: Forrest plot comparing change in BCVA (letters) in the early phase (≤6 months) in the anti-VEGF treatment group compared to the other treatment groups. © Dipl.-Ing. Embacher Stefan

Only two studies (one two arm, one three arm study) provide results examining the CRT in the early phase resulting in a simple network structure (see Figure 4).

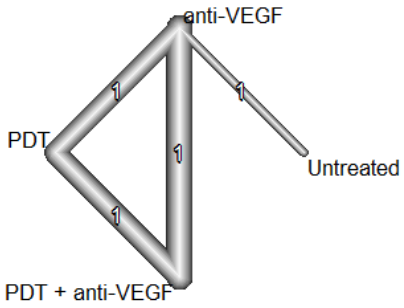

Figure 4: Network graph comparing the structure of the network regarding different treatments based on CRT in the early phase (≤6 months). © Dipl.-Ing. Embacher Stefan

The small number of studies comparing CRT show similar results to the analysis of BCVA. Anti-VEGF treatment led to a significant decrease in CRT compared to untreated patients (66.8 µm; 95 % CI, 40.2-93.4; p<0.0001) as well as in patients treated with PDT (27.7 µm; 95 % CI, 16.1–39.3; p<0.0001). The combination treatment of PDT and anti-VEGF therapy resulted in a significant larger decrease in CRT than in patients treated solely with anti-VEGF (12.0 µm; 95 % CI, 21.4-2.6; p=0.013) (see Figure 5). Because of the small number of included studies inconsistency was not assessed.

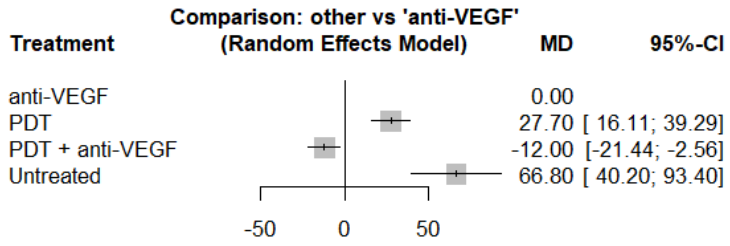

Figure 5: Forrest plot comparing change in CRT in the early phase (≤6 months) in the anti-VEGF treatment group compared to the other treatment groups. © Dipl.-Ing. Embacher Stefan

3.4 Outcome in the later phase (>6 months)

The evidence network of the long-term results of BCVA comprises fifteen studies, comparing six different arms (see Figure 6).

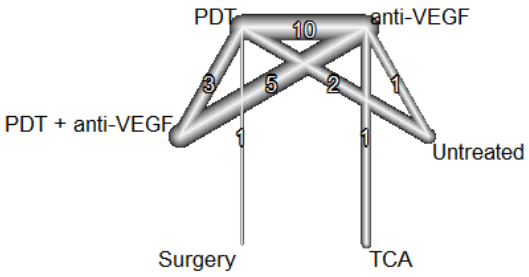

Figure 6: Network graph comparing the structure of the network regarding different treatments based on BCVA in the later phase (>6 months). © Dipl.-Ing. Embacher Stefan

The favorable outcome of the anti-VEGF group compared to the untreated group in the early phase could be maintained in the long-term with a mean estimated gain of 28.4 letters (95 % CI, 22.7-34.1; p<0.0001). The anti-VEGF group had a tendency to gain estimated 13.1 letters (95 % CI, 9.7-16.5; p<0.0001) more compared to the PDT group. Further, the anti-VEGF treatment led to better, but insignificant results in comparison to the TCA group with a gain of 7.5 letters (95 % CI, -1.0-16.0; p=0.084). The anti-VEGF group had similar results to the combination group (PDT and anti-VEGF) (-0.02; 95 % CI, -3.9-3.8; p=0.991). Similarly, when comparing the surgical and anti-VEGF groups, the gain of 9.9 letters (95 % CI, -11.3-31.1; p=0.359) in the surgical group remained insignificant (see Figure 7). Further, no inconsistency in the network was observed (p=0.113).

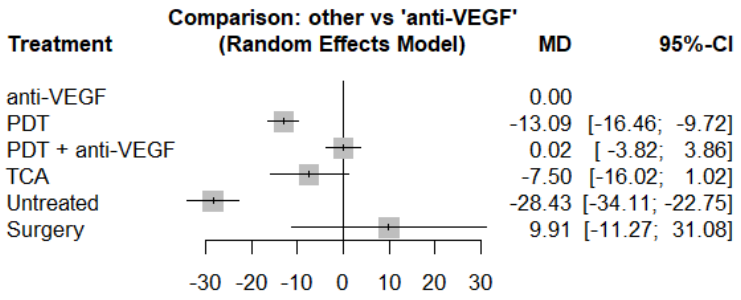

Figure 7: Forrest plot comparing change in BCVA in the later phase (>6 months) in the anti-VEGF treatment group compared to the other treatment groups. © Dipl.-Ing. Embacher Stefan

The four studies comparing the effect of three treatments on the CRT in the later phase show a triangle shape in the network structure (see Figure 8).

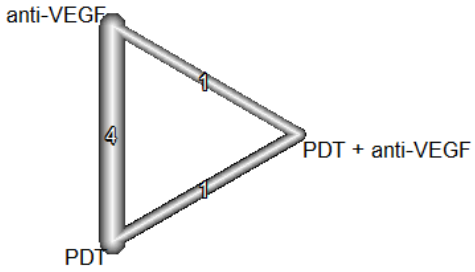

Figure 8: Network graph comparing the structure of the network regarding different treatments based on CRT in the later phase (>6 months). © Dipl.-Ing. Embacher Stefan

There were no differences between the groups regarding the long-term outcomes of CRT. There was no difference when comparing the anti-VEGF group to the PDT group (10.4 µm; 95 % CI, -37.1-57.8; p=0.669) and to the combination (PDT and anti-VEGF) group (25.3 µm; 95 % CI, -56.7-107.2; p=0.546; see Figure 9). Also, there was no sign of inconsistency (p=0.002).

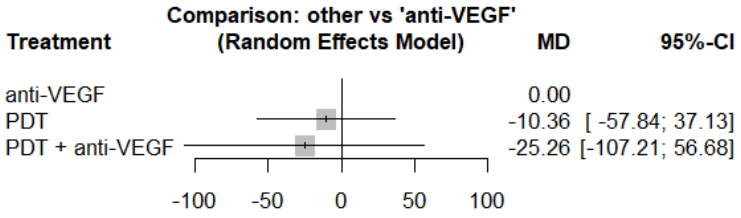

Figure 9: Forrest plot comparing change in CRT in the later phase (>6 months) in the anti-VEGF treatment group compared to the other treatment groups. © Dipl.-Ing. Embacher Stefan

3.5 Differences in anti-VEGF drugs

In the early phase eight studies and in the later phase thirteen studies were compared regarding the change in BCVA after treatment with different anti-VEGF drugs. The early outcome of patients receiving bevacizumab were similar compared to aflibercept (p=0.222), ranibizumab (p=0.124) and conbercept (p=0.572). The same applies to the results in the late phase (p=0.250, p=0.265, respectively p=0.382).

There were five studies examining the CRT for both time points. A significant larger decrease in CRT was found in the aflibercept group compared to bevacizumab (12.1 µm; 95 % CI, 3.0-21.2; p=0.009). There was no significant difference in the change

of CRT between bevacizumab compared to ranibizumab (7.6 µm; 95 % CI, -13.3-28.5; p=0.477) and to conbercept (-5.4 µm; 95 % CI, -41.5-30.8; p=0.771). Regarding the long-term results, no significant difference between the various anti-VEGF factors could be found.

3.6 Treatment strategies

Concerning the BCVA there were four studies (earlier phase) and seven studies (later phase) comparing the 1+PRN and 3+PRN treatment strategies. No significant differences could be detected. In the earlier phase, patients treated with 3+PRN gained 0.8 letters (95 % CI, -2.8-4.5; p=0.652). In the later phase, there was an insignificant gain of 0.7 letters in patients treated with 1+PRN (95 % CI, -2.3-3.8; p=0.635) compared to the 3+PRN group.

Regarding the anatomical recovery (three studies earlier phase and five studies later phase), there were no significant differences in the CRT found. In the short-term results, the CRT decreased insignificantly by 20.0 µm (95 % CI, -4.6-44.7; p=0.111) in patients treated by 3+PRN compared to patients treated with 1+PRN. In the long-term results, the CRT decrease of 3.2 in the 3+PRN group (95 % CI, -15.1-21.4; p=0.734) was insignificant compared to the 1+PRN group.

In contrast, the number of injections showed significant differences. While patients assigned to the 1+PRN group received 1.8 (SD 1.3) injections during a twelve months period, the 3+PRN group received 3.2 (SD 0.9) injections (p<0.0001). Further, the injection number between patients receiving PDT + anti-VEGF versus solely anti-VEGF were compared. Combination treatment required 2.2 (SD 1.5), whereas patients receiving only anti-VEGF treatment required 2.6 (SD 1.3) injections. This difference was not significant (p=0.155).

3.7 Other Treatments

There were two studies (22, 23) that reported on surgical interventions as a treatment option for myopic CNV. A total of sixty-four eyes were observed, in eighteen eyes surgical removal and in forty-six translocation was performed. The study by Glacet-Bernard et al (22) showed a positive effect in the translocation group (n=32), the visual acuity improved from 35 to 55 letters after three months, whereas the PDT treatment group (n=34) achieved worse results. Also, the study by Hamelin et al (23) observed an increase of 48.5 letters (mean follow-up fourteen months) in the surgical removal group (n=18) and a gain of 31 letters in the translocation group (n=14) (follow-up eleven months).

There was one study (55) investigating the use of oral bisphosphonates. BCVA increased significantly in the group taking oral bisphosphonates compared to the untreated group. In detail, the bisphosphonate group gained 14 letters (21 eyes, $p=0.032$), the PDT group 13 letters (20 eyes, $p=0.021$) and the anti-VEGF group 19.5 letters (37 eyes, $p<0.001$).

One study by Kobayashi et al (37) investigated the use of radiotherapy. The analysis of the outcome after treatment with radiotherapy in twenty eyes compared to nineteen untreated eyes was conducted. The BCVA slightly increased from 37.1 letters at baseline to 38.9 letters in a three months period and then decreased to 36.1 letters after two years whereas, the control group showed a BCVA decrease after two years.

One study investigating the use of laser treatment showed an insignificant BCVA decrease in a two-year period (baseline 62.5 and two-year follow-up 57 letters). The PDT group performed similarly with a BCVA decrease from 59 letters at baseline to 49 letters ($p=0.002$). While the anti-VEGF group records a BCVA increase from 54.5 letters to 64 letters ($p=0.006$) (27).

Sub-Tenon TCA was compared to bevacizumab by Wakabayashi et al (56). The BCVA of twenty eyes receiving sub-Tenon TCA worsened by 1.5 letters, while the thirty-four eyes treated with bevacizumab improved by 9 letters ($p<0.001$) after twelve months.

4 Discussion

4.1 Interpretation of Results

The key-message of this network meta-analysis is, that intravitreal anti-VEGF using the 1+PRN regimen is an effective treatment of myopic CNV with good short- and long-term results.

4.1.1 Anti-VEGF

Anti-VEGF treatment is the gold standard treatment for myopic CNV, which is supported by the results of this network meta-analysis. It leads to an improvement in visual acuity in the short- and long-term.

In diabetic macular edema, different anti-VEGF factors are considered more effective than others. Aflibercept showed a greater improvement in visual acuity in patients with low baseline BCVA (<69 letters) (57). Therefore, a subgroup analysis comparing different VEGF inhibitors such as bevacizumab, ranibizumab, aflibercept and conbercept was carried out. This network meta-analysis, however, could not detect any difference between the VEGF inhibitors. Only aflibercept led to a larger decrease in CRT, but without having an impact on visual acuity. This should lead to further scientific investigation.

A further subgroup analysis regarding the anti-VEGF treatment regimen was carried out. Thereby, no difference in letters gained, could be demonstrated whether three injections were administered consecutively as loading dose or only one. However, the 1+PRN group required significantly less injections than the 3+PRN group. This result could signify, that the 3+PRN treatment strategy implies an overtreatment. Future research should investigate this further.

4.1.2 PDT + Anti-VEGF

Although the combination therapy of PDT and anti-VEGF led to a marginally higher decrease of CRT than the solely anti-VEGF treatment in the early phase, the absolute difference of 12 µm is likely to be clinically insignificant. In the later phase however, the CRT did not differ between the two groups. There was no significant difference in visual acuity between patients treated with anti-VEGF and the combination of PDT and anti-VEGF.

There was also no difference in the number of injections within twelve months. Taking the non-differing results as well as the absence of randomized controlled trials into consideration, anti-VEGF monotherapy seems the more reasonable first-line treatment.

4.1.3 TCA

Intravitreal TCA was inferior to anti-VEGF in improving visual acuity in the short-term. In the long-term, there was no difference in the anti-VEGF and the TCA group. Intravitreal TCA is known to cause an IOP (intra ocular pressure) increase in nearly one-third of all patients and has a high prevalence of cataract formation and progression over time (56, 58). Taking these side effects into consideration, intravitreal anti-VEGF appears to be the more beneficial choice.

4.1.4 PDT

In this network meta-analysis PDT, which was the previous gold standard for treating myopic CNV, was shown to be inferior to the anti-VEGF treatment. Patients treated with PDT had a significantly lower gain of letters over all time periods.

4.1.5 Other treatments

Some treatments could not be included in the quantitative network meta-analysis, because of too small sample sizes and/or too few studies.

Laser photocoagulation may lead to a significant decrease in macular edema with subsequent increase in visual acuity. However, it may lead to many complications such as laser scarring (59).

Surgical intervention may also improve visual acuity, but carry the risk of serious short- and long-term complications and has large treatment costs. Further, surgical treatments show a high percentage of CNV recurrence (surgical removal 39 % and translocation 14 %) (23).

One study investigated the effect of oral bisphosphonates on myopic CNV (55). Bisphosphonates are hypothesized to have an antiangiogenic impact by suppressing VEGF (60). Visual improvement was similar to PDT, but worse than anti-VEGF (55). Since common side effects of their long-term use include

hypocalcemia, bone pain, and osteonecrosis of the jaw, bisphosphonate treatment does not seem a reasonable alternative (61).

4.2 Complications

The risk of complications could not be quantified as most studies did not report on complications. Complication rates are listed in Supplementary Table 2. However, not all studies specifically tested or asked for complications.

The highest complication rates were found in the surgical intervention group (22, 23). Intravitreal steroids showed an increase of IOP and progression of cataract, both known side effects (56, 58). After intravitreal VEGF inhibitor injection, some patients experienced corneal erosions and dry eye symptoms (28, 62). Most studies did not report on these adverse events. Similarly, most studies did not measure IOP after injection so a presumptive IOP elevation could not be detected. Furthermore, four cases of retinal detachment after intravitreal injection (29, 63, 64) and one (0.0004 %) case of sterile vitritis (65) was reported.

4.3 Limitations

This network meta-analysis shows several limitations. First, there was a high degree of heterogeneity in patients' characteristics, probably caused by different inclusion and exclusion criteria (see Supplementary Table 1). Some studies included pretreated patients and some only untreated patients. Further, patients who had undergone previous vitreous surgery, which might impact the effect of intravitreal anti-VEGF, were either included or excluded in the various studies. As there is no common definition for pathologic myopia, the studies might include slightly different patient populations. Further, the definition of myopic CNV was sometimes not reported, making a comparison even more difficult.

Second, the studies reported their outcomes at different timepoints, which led to different follow-up periods. Some studies reported on results after one month, three months or six months. There has been too little data to compare the exact time points. In order to compare the different follow-up data, the data was summarized assuming that the different time points were effectively the same. To create better comparability priority was given to certain time points. In the early phase, priority was given to the outcome after three months, then six months and as a last option

one month. In the later phase, priority was given first to twenty-four months, then twelve months, and as a last option, all follow-up time points after twenty-four months. However, the classification of follow-up dates might bias our results.

Third, the search was restricted to English-language publications, overlooking some possibly relevant studies.

Then, the BCVA as a main outcome was measured in different ways in the included studies. Not all studies used the EDTRS (Early Treatment Diabetic Retinopathy Study) charts for visual acuity testing, which required a conversion to the letter score. The CRT as a second outcome was not reported in all studies and different OCT (optical coherence tomography) devices were used, making comparison difficult and weakening the validity of the results.

Finally, the inclusion of different study designs, such as randomized controlled trials and observational studies, could result in non-compatible data. In addition, including non-randomized trials could lead to potential bias within the individual study. Based on visual inspection of funnel plots and analytical methods, we did not observe signs of publication bias.

4.4 Conclusion

This network meta-analysis confirms that the first-line therapy for myopic CNV is intravitreal injection of VEGF inhibitors. This therapy surpasses all other investigated treatment options. Only the combination treatment of PDT and anti-VEGF led to a marginally better, but most-likely clinical insignificant result regarding the CRT in the early phase. Contrary to other entities (for example diabetic macular edema) the different anti-VEGF drugs appear equally effective in treating myopic CNV. The use of the 1+PRN regimen seems reasonable to keep the number of injections low.

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Attachment

Table 1: Table of study characteristic and inclusion criteria of all 63 studies included for qualitative analysis.

ID-Study	Randomized	N	Treatment	Country of Origin	Definition of myopic CNV	Min. Axial length	Inclusion Criteria	Exclusion Criteria	Pre-treatment
Baba, 2010 (41)	No	12 12	Bevacizumab PDT	Japan	i) <-6 diopters ii) Type 2 juxta- and subfoveal CNV, active on FLA	n/d	i) follow-up >2 years ii) initial onset of symptoms <6 months	i) BCVA<0.1 (baseline) ii) age <40 years	No
Bandello, 2003 (66)	No	12 13	PDT Untreated	Italy	i) ≤-6 diopters ii) AL ≥26.5 mm	≥26.5 mm	i) active extrafoveal CNV on FA ii) previously treatment with laser photocoagulation iii) retinal abnormalities iv) <5400 μm CNV dimension	i) other potential causes of CNV	Yes
Bandello, 2013 (62)	Yes	222 55	Ranibizumab PDT	Multicenter	VIP study	n/d	n/d	n/d	n/d
Brancato, 1988 (42)	Yes	9 9 9	Laser (577) Laser (590) Laser (620)	n/d	i) <-6 diopters ii) CNV documented with FLA <7 days iii) minimal distance of 100 microns from center of the foveal avascular zone	No	i) BCVA ≥0.1	i) other ocular disease that could modify FLA	No
Brilliance Study, 2019 (29)	Yes	182 184 91	Ranibizumab VA guided Ranibizumab Disease guided PDT	Multicenter 5 countries	i) <-6 diopters ii) AL≥26 mm iii) myopic changes CNV leakage in FLA iv) intra-or subretinal fluid v) Increase in central subfield thickness	≥26 mm	i) BCVA ≥24 to ≤78	i) nAMD ii) histoplasmosis iii) polypoidal choroidal vasculopathy iv) active infectious disease v) intraocular inflammation vi) infection vii) increased IOP viii) RVO ix) Diabetes mellitus x) severe DR xi) arterial hypertension xii) stroke or myocardial infarction within 3 months xiii) PRP within 6 months xiv) focal macular laser at any time xv) anti-VEGF or PDT at any time xvi) intravitreal corticosteroids or surgery within 3 months xvii) pregnant women	No

Calvo-González, 2017 (67)	No	26 35	Ranibizumab 1+PRN Ranibizumab 3+PRN	n/d	i) <-6 diopters ii) AL >26.0mm iii) retinal abnormalities iv) active sub- or juxtafoveal CNV	>26 mm	n/d	i) PDT within 6 months ii) prior anti-VEGF treatment iii) CNV due to other cause iv) previous thromboembolic episodes v) allergy to fluorescein vi) fertile women not using contraception vii) follow-up < 24 months	Yes
Cha, 2014 (43)	No	23 43	Ranibizumab Bevacizumab	South Korea	i) >26 mm AL ii) < -6 diopters iii) pathologic myope	>26 mm	i) no pretreatment ii) BCVA 20/500-20/30 iii) >12months follow-up	i) history of intraocular surgery except cataract ii) cataract surgery <6 months before enrollment iii) other ocular disorder decreasing visual acuity iv) cataract surgery or YAG capsulotomy during follow-up	No
Chan, 2007 (58)	No	22 22	PDT + TCA PDT	n/d	i) ≤-6 diopters ii) sub- or juxtafoveal CNV iii) leakage in FLA iv) greatest linear dimension <5400um	n/d	i) BCVA ≥ 20/400	i) CNV due to other causes ii) prior treatment iii) history of glaucoma	No
Chen, 2011 (39)	No	17 6	Bevacizumab PDT + Bevacizumab	USA	i) myopic CNV	n/d	n/d	n/d	n/d
Chen, 2020 (68)	No	31 33	Conbercept Ranibizumab	China	n/d	>26 mm	i) BCVA >20/800 ii) >18years	i) CNV secondary t other causes ii) other chorioretinopathies iii) history of prior treatment	No
Costa, 2006 (69)	Yes	8 8	PDT standard 50J/cm^2 PDT two-fold 100J/ cm^2	Brazil	i) <-6 diopters or AL≥26 mm ii) retinal abnormalities iii) CNV under foveal avascular zone	≥26.5 mm	n/d	i) drusen ii) traumatic choroidal rupture iii) peripapillary changes with atrophic or pigmented "punched out chorioretinal lesions iv) uveitis v) any other ophthalmic disorder that might affect visual function vi) disability to cooperate vii) allergy to fluorescein viii) porphyria ix) previous treatment for CNV x) significant opacities	No

Dethorey, 2010 (70)	No	19 34	Ranibizumab PDT	France	i) ≤-6 diopters or AL≥26 mm ii)myopic CNV	≥26.5 mm	n/d	n/d	No
El Habbak, 2016 (71)	Yes	10 10	Ranibizumab Aflibercept	Egypt	n/d	n/d	n/d	n/d	n/d
Erden, 2019 (40)	No	12 18	Aflibercept Ranibizumab	Turkey	i) <-6 diopters or AL>26 mm ii) and myopic CNV	>26 mm	n/d	i) CNV due to other causes ii) uncontrolled glaucoma iii) history of photocoagulation or PDT iv) iris neovascularization v) vitreous hemorrhage vi) history of thromboembolic events	Yes
Farinha, 2013 (72)	No	11 8 9	PDT Ranibizumab PDT + Ranibizumab	Portugal	i) ≤-6 diopters or AL≥26 mm ii) myopic CNV	≥26 mm	i) contralateral myopia without CNV ii) minimum follow-up of 3 years	i) amblyopia ii) glaucoma iii) uveitis iv) dense cataract v) diabetic retinopathy vi) retinal vascular abnormalities vii) laser treatment viii) intravitreous injection of triamcinolone ix) previous vitrectomy and scleral buckling	No
Fernandez, 2013 (73)	No	8 8	Ranibizumab Bevacizumab	Spain	n/d	n/d	i) subfoveal	n/d	n/d
Fonseca, 2010 (74)	No	25 19	Bevacizumab Ranibizumab	Portugal	n/d	n/d	n/d	n/d	n/d
Freitas-da-Costa, 2014 (65)	No	67 IVB + IVR	Bevacizumab Ranibizumab	Portugal	i) <-6 diopters ii) with retinal abnormalities or AL ≥26.5 mm iii) CNV active disease with leakage in FLA	≥26.5 mm	i) treatment with IVB ii) and/or IVR	i) CNV secondary to other causes ii) retinal vascular disease iii) intraocular surgery during period of study	Yes

Gharbiya, 2010 (18)	Yes	16 16	Ranibizumab Bevacizumab	Italy	i) AL >26.5 mm ii) CNV	>26.5 mm	i) leakage from FLA	i) other ocular disease that could affect BCVA ii) angioid streaks iii) trauma iv) choroiditis v) hereditary diseases vi) aphakia vii) previous vitreoretinal surgery viii) prior history of bleeding diathesis ix) prior cerebrovascular accident x) pulmonary embolus or deep venous thrombosis xi) myocardial infarction xii) uncompensated CAD within 6 months xiii) major surgery within 6 weeks xiv) uncontrolled hypertension	No
Glacet-Bernard, 2007 (22)	No	34 32	PDT Translocation	France	i) ≤-6 diopters ii) AL ≥26.5 mm	≥ 26.5 mm	i) subfoveal CNV ii) BCVA 20/40 iii) and 20/100 for PDT iii) and ≤ 20/63 for translocation	n/d	Yes
Hamelin, 2002 (23)	No	18 14	Surgical Removal Translocation	France	n/d	n/d	i) subfoveal CNV	n/d	n/d
Hayashi, 2008 (75)	No	22 66	PDT Untreated	Japan	i) ≤-6 diopters ii) AL ≥26.5 mm	≥26.5 mm	i) greatest linear dimension of CNV lesion <5400um ii) active CNV iii) FU>6months	i) other ocular disease such as large drusen ii) multifocal choroiditis iii) punctate inner choroidopathy iv) active hepatitis v) clinically significant liver disease vi) earlier CNF treatment vii) porphyria viii) intraocular surgery within 2 months	No
Hayashi, 2009 (76)	No	43 44 74	Bevacizumab PDT Untreated	Japan	i) ≤-6 diopters ii) AL ≥26.5 mm	≥26.5 mm	i) FLA leakage from CNV ii) FU>1year	n/d	Yes

Howaidy, 2021 (77)	Yes	24 24	Aflibercept Ranibizumab	Egypt	i) ≤-6 diopters ii) AL ≥26 mm ii) active CNV in FLA	≥26 mm	i) patient complaint <8weeks ii) clear ocular media	i) previous vitreoretinal intervention ii) associated retinal disorders (e.g., angioid streaks and choroiditis) iii) coexisting macular pathology secondary to pathologic myopia (e.g., myopic tractional maculopathy and myopic macular hole) iv) myocardial infarction v) thromboembolic events <6 months	No
Iacono, 2012 (26)	Yes	23 25	Ranibizumab Bevacizumab	Italy	i) ≤-6 diopters ii) AL ≥26.5 mm	≥26.5 mm	i) baseline BCVA 20/32 ii) and 20/400 iii) >12 months iv) post menopause	i) intraocular surgery <6months ii) any other ocular disease that could compromise vision iii) ocular hypertension iv) glaucoma v) uncontrolled systemic hypertension vi) peripheral vascular disease vii) history of thromboembolism viii) ischemic heart disease ix) stroke	No
Iacono, 2017 (78)	No	15 33	Bevacizumab Ranibizumab	Italy	i) ≤-6 diopters ii) AL ≥26.5 mm	≥26.5 mm	i) sub- and juxtafoveal CNV ii) FLA iii) >12months iv) post menopause v) fertile women using contraception	i) previous anti-VEGF ii) intraocular surgery <6 months iii) any other ocular surgery that could compromise vision in the study eye iv) pregnancy v) ocular hypertension vi) glaucoma vii) uncontrolled systemic hypertension viii) peripheral vascular disease ix) history of thromboembolism x) stroke	No
Ikuno, 2010 (79)	No	11 20	Bevacizumab PDT	Japan	i) ≤-6 diopters ii) AL ≥26.5 mm	≥26.5 mm	i) women ii) >50a iii) active sub- or juxtafoveal iv) no history of pretreatment v) baseline BCVA 20/200-20/40 vi) baseline CNV size 1200-3000um	i) history of vitrectomy ii) intraocular surgery other than cataract iii) presence of macular hole iv) retinal detachment v) foveoschisis vi) severe cataract vii) symptom duration >24months viii) significant glaucoma detected by visual field loss	No

Introini, 2012 (80)	No	13 9	Bevacizumab Ranibizumab	Italy	i) <-6 diopters	n/d	i) BCVA >20/200	i) presence of retinal diseases ii) previous CNV treatment iii) intraocular surgery within the last 3 months iv) glaucoma v) pregnancy vi) uncontrolled systemic hypertension vii) history of thromboembolic disease viii) ischemic cardiovascular disease	No
Kang, 2017 (81)	No	17 20	Bevacizumab PDT	Korea	n/d	n/d	n/d	n/d	n/d
Kobayashi, 2000 (37)	Yes	20 19	Radiotherapy Untreated	Japan	i) ≤-8 diopters ii) AL ≥26 mm	≥26 mm	i) VA <0.4, subfoveal ii) age >60	i) other ocular disease such as glaucoma, chronic inflammation or neoplastic disorder ii) systemic diseases (diabetes, uncontrolled hypertension, known life threatening disease)	n/d
Korol, 2020 (36)	Yes	50 47	Ranibizumab Aflibercept	Ukraine and Arab Emirates	i) ≤-6 diopters ii) AL ≥26.5 mm	≥26 mm	i) new onset of myopic CNV <2 months ii) age <18 a	i) other ocular disease (CNV, ocular inflammation, glaucoma, ocular hypertension, opacity) ii) pregnancy iii) lactation iv) disability to provide informed consent	n/d
Lai, 2012 (64)	No	22 15	Bevacizumab Ranibizumab	China	i) <-6 diopters	n/d	i) follow-up>2 years ii) subfoveal CNV iii) BCVA >20/800 iv) FA leakage	i) prior treatment ii) secondary CNV to other ocular disease	No
Li, 2019 (63)	Yes	26 24	Ranibizumab 1+PRN Ranibizumab 3+PRN	China	i) ≤-6 diopters ii) AL ≥26 mm	≥26 mm	i) active sub- or juxtafoveal CNV in FLA ii) baseline BCVA 24-73	i) presence of other ocular disease that affected VA ii) anti-VEGF within 6 months iii) previous PDT iv) intraocular surgery within 3 months v) uncontrolled glaucoma vi) pregnancy vii) severe systemic condition (uncontrolled hypertension, history of thromboembolic or ischemic cardiovascular disease)	Yes

Matsuo, 2012 (35)	No	22 20	Anti-VEGF PDT	Japan	i) ≤-6 diopters ii) AL ≥26 mm	≥26 mm	i) active sub- or juxtafoveal CNV in FLA ii) visual symptoms iii) onset within 6 months iv) minimum follow-up 6 months	i) history of RVO ii) uveitis iii) rhegmatogenous retinal detachment iv) glaucoma	No
Miki, 2013 (55)	No	37 20 21 22	Anti-VEGF PDT Bisphos-phonates Untreated	Japan	i) ≤-6 diopters ii) AL ≥26 mm	≥26 mm	i) subretinal lesions ii) hemorrhage	n/d	No
Myrror Study, 2015 (38)	Yes	90 31	Aflibercept Sham/ Placebo	Japan	i) ≤-6 diopters ii) AL ≥26 mm	≥26.5 mm	i) active CNV ii) BCVA 73-35 letters	i) 1 functional eye ii) recurrent myopic CNV iii) aphakia iv) history of CNV with other origin v) ocular inflammation vi) NVI vii) vitreous hemorrhage viii) uncontrolled glaucoma ix) previous filtration surgery x) pregnant women xi) breast-feeding women	No
Ng, 2015 (50)	No	77 16	Bevacizumab 3+PRN Bevacizumab 1+PRN	China	i) ≤−6.0 diopters	n/d	i) follow-up >1year ii) evidence of leakage on FA	i) PDT or triamcinolone during follow-up ii) CNV secondary to AMD or other causes such as trauma, choroiditis, angioid streaks and hereditary disease iii) cataract or refractive surgery during follow-up iv) history of vitrectomy v) serious posterior segment complications such as retinal detachment or foveoschisis vi) history of previous anti-VEGF treatment	Yes
Niwa, 2012 (82)	No	13 19	Bevacizumab 1+PRN Bevacizumab 3+PRN	Japan	i) ≤-6 diopters ii) AL ≥26 mm	≥26.5 mm	n/d	i) other causes of CNV ii) previous treatment	No
Pal, 2010 (83)	No	22 8 21	Untreated PDT Anti-VEGF	London	n/d	n/d	n/d	n/d	n/d

Parodi, 2010 (27)	Yes	18 17 19	PDT Krypton Laser Photo-coagulation Bevacizumab	Italy	i) ≤-6 diopters ii) AL ≥26 mm iii) and retinal abnormalities	≥26 mm	i) juxtafoveal CNV on FA ii) >5400um CNV size iii) BCVA 20/200 to 20/40 iv) symptoms <1 month v) documented visual acuity deterioration	i) any other condition associated with CNV ii) any significant ocular disease that could compromise vision iii) active hepatitis iv) clinically significant liver disease v) peripheral vascular disease vi) thromboembolism vii) stroke viii) intraocular surgery <2 months ix) pervious laser photocoagulation	n/d
Parravano, 2014 (32)	No	43 42	PDT Ranibizumab	Italy	i) ≤-6 diopters	n/d	i) follow-up >1year	n/d	No
Pece, 2015 (33)	Yes	40 38	Bevacizumab Ranibizumab	Italy	i) ≤-6 diopters	n/d	i) myopic retinal changes of posterior pole ii) FA active CNV iii) BCVA >20/400 at baseline iv) duration of symptoms <4 weeks v) clear ocular media	i) retinal disease other than myopia ii) extrafoveal CNV iii) other chorioretinal alterations iv) refractive media opacities v) recent myocardial infarction vi) thromboembolic events vii) previous intravitreal injections	No
Radiance Study, 2014 (28)	Yes	106 116 55	Ranibizumab VA guided Ranibizumab Disease guided PDT	Inter-national	i) ≤-6 diopters ii) and/or AL ≥26 mm	≥26 mm	i) active leakage from CNV ii) presence of retinal or subretinal fluid iii) or increase in retinal thickness iv) BCVA 24-78	i) history of stroke ii) history of retinal or focal laser photocoagulation iii) intraocular treatment with corticosteroid iv) surgery within prior 3 months v) hypersensitivity to ranibizumab vi) CNV secondary to other causes vii) active infectious disease viii) intraocular inflammation ix) IOP >25 mmHg x) iris neovascularization xi) pregnant or nursing women	No

Rinaldi, 2017 (34)	Yes	20 20 20	PDT PDT + Ranibizumab Ranibizumab	Italy	i) ≤-6 diopters ii) and/or AL ≥26 mm iii) and retinal abnormalities	≥26 mm	i) FA sub or juxtafoveal CNV ii) clear ocular media iii) duration of iv) symptoms <4weeks	i) prior treatment ii) presence of another maculopathy iii) history of myocardial infarction iv) thromboembolic event v) uncontrolled hypertension vi) uncontrolled glaucoma vii) refractive media opacities viii) ocular surgery	No
Rishi, 2011 (31)	No	11 3 5 4 3	PDT PDT + TCA PDT+ Bevacizumab PDT + Ranibizumab PDT + Ranibizumab reduced fluence	India	i) ≤-6 diopters	n/d	i) active CNV on FA	n/d	n/d
Rishi, 2016 (30)	No	23 25 31	PDT Anti-VEGF PDT + Anti-VEGF	India	i) ≤-6 diopters	n/d	n/d	n/d	n/d
Ruiz-Moreno, 2011a (24)	Yes	28 27	PDT Bevacizumab	Spain	i) ≤-6 diopters ii) and/or AL ≥26 mm	≥26 mm	i) <18 a ii) active sub- and juxtafoveal CNV iii) decreased VA iv) attributable to CNV	i) previous vitrectomy ii) tractional maculopathy iii) pregnant women iv) fertile women not willing to use contraception	n/d
Ruiz-Moreno, 2011b (84)	No	19 20	Bevacizumab 3+PRN Bevacizumab 1+PRN	Spain	n/d	n/d	n/d	n/d	
Ruiz-Moreno, 2012 (85)	No	107 32	Bevacizumab 1+PRN Bevacizumab 3+PRN	Spain and Portugal	n/d	n/d	n/d	n/d	Yes
Ruiz-Moreno, 2013a (86)	No	53 24	Bevacizumab Ranibizumab	Spain and Portugal	i) ≤-6 diopters ii) and/or AL ≥26 mm	≥26 mm	n/d	i) retinal Drusen ii) AMD	Yes
Ruiz-Moreno, 2013b (87)	Yes	28 27	PDT Bevacizumab	Spain	i) ≤-6 diopters ii) and/or AL ≥26 mm	≥26 mm	i) <18 a ii) active sub- or juxtafoveal CNV iii) decreased VA attributable to CNV	i) previous vitrectomy ii) tractional maculopathy iii) pregnant women iv) fertile women not willing to use contraception	n/d

Ruiz-Moreno, 2015 (88)	No	78 19	Bevacizumab Ranibizumab	Spain and Portugal	i) ≤-6 diopters ii)and/or AL ≥26 mm iii) and/or fundus changes of high myopia	≥26 mm	n/d	i) less than 6-year follow-up ii) retinal drusen iii) AMD iv) previously vitrectomised v) treated for mCNV with two or more intravitreal drugs or PDT	Yes
Saviano, 2014 (89)	No	17 17	PDT + Bevacizumab Bevacizumab	Italy	i) ≤-6 diopters ii) and/or AL ≥26 mm	≥25 mm	n/d	i) membranes correlated to pathologic myopia ii) glaucoma iii) intolerance to medication used	Yes
Sayanagi, 2019 (90)	No	12 15	Ranibizumab Aflibercept	Japan	i) ≤-6 diopters ii) and/or AL ≥26 mm	≥26.5 mm	i) sub- or juxtafoveal CNV	i) treatment other than anti-VEGF before or during observation ii) follow-up <6 months iii) intraocular surgery other than cataract surgery iv) other ocular diseases during follow-up	No
VIP-Report-1, 2001 (19)	Yes	81 39	PDT Sham/ Placebo	Multicenter	i) <-6 diopters ii) with retinal abnormalities iii) AL >26.5 mm	>26.5 mm	i) CNV under FAZ ii) CNV>50 % of total neovascular lesion iii) <5400um CNV size iv) BCVA≥50	i) any other condition associated with CNV ii) RPE tear iii) any ocular disease compromising vision iv) history of CNV other than no foveal confluent laser photocoagulation v) prior PDT vi) IOL surgery within last 2 months vii) active hepatitis viii) porphyria ix) participation in other clinical trial x) pregnancy	Yes
VIP-Report-3, 2003 (21)	Yes	81 39	PDT Sham/ Placebo	Multicenter	i) <-6 diopters ii) with retinal abnormalities iii) AL >26.5 mm	>26.5 mm	i) CNV under FAZ ii) CNV>50 % of total neovascular lesion iii) <5400um CNV size iv) BCVA≥50	i) any other condition associated with CNV ii) RPE tear iii) any ocular disease compromising vision iv) history of CNV other than no foveal confluent laser photocoagulation v) prior PDT vi) IOL surgery within last 2 months vii) active hepatitis viii) porphyria ix) participation in other clinical trial x) pregnancy	Yes

Voykov, 2010 (91)	No	11 10	Bevacizumab PDT + Bevacizumab	Germany	i) ≤-6 diopters	n/d	i) sub- or juxtafoveal CNV ii) BCVA >20/400	i) CNV secondary to other causes in study or fellow eye	Yes
Wakabayashi, 2009 (56)	No	20 34	Sub-tenon TCA Bevacizumab	Japan	i) ≤-6 diopters	n/d	i) active CNV on FA	i) extrafoveal CNV ii) BCVA <20/200 iii) previous treatment such as PDT or photocoagulation iv) history of cataract v) vitreous surgery	No
Wakabayashi, 2011 (92)	No	19 12	Bevacizumab 1+PRN Bevacizumab 3+PRN	Japan	i) ≤-6 diopters ii) and/or AL ≥26 mm	≥26.5 mm	i) newly developed and active mCNV	i) <20/200 BCVA ii) history of scleral buckling iii) vitreous surgery iv) other treatments such as photodynamic therapy and photocoagulation	No
Wang, 2018 (93)	No	36 42	Aflibercept Bevacizumab	Taiwan	i) >26 mmHg	≥26 mm	i) treatment-naïve ii) >18 a iii) BCVA 20/400-20/40	i) pregnant ii) nursing iii) history of thromboembolic events iv) major surgery within previous 3 months v) uncontrolled hypertension vi) known coagulation abnormalities v) use of anticoagulants other than aspirin vi) prior macular photocoagulation or PDT vii) prior intraocular surgery within 3 months viii) active infectious disease or inflammation ix) intraocular pressure >25 mmHg x) presence of iris neovascularization xi) vitreous hemorrhage	No
Woronkowicz, 2018 (94)	No	85 125	Bevacizumab Ranibizumab	United Kingdom	n/d	n/d	n/d	n/d	n/d
Yoon, 2010 (95)	No	51 63 28	PDT Anti-VEGF PDT + Anti-VEGF	Korea	i) ≤-6 diopters ii) and/or AL ≥26 mm	≥26.5 mm	i) active CNV on FLA ii) BCVA >20/400 iii) follow-up >12months	i) prior laser photocoagulation on study eye ii) radiation on study eye iii) vitrectomy on study eye iv) history of subtenon injection of triamcinolone acetonide v) PDT or anti-VEGF within 6 months vi) cataract surgery during follow-up vii) presence of comorbid ocular conditions	Yes

Yoon, 2012 (96)	No	14 26	Ranibizumab Bevacizumab	Korea	i) ≤-6 diopters ii) and/or AL ≥26 mm	≥26.5 mm	i) active CNV on FLA ii) BCVA >20/400 iii) follow-up >12months iv) sub- or juxtafoveal CNV	i) history of previous treatment ii) cataract surgery within follow-up period iii) presence of comorbid ocular conditions that might affect VA	Yes

Table 2: Table of complication rates for all 63 studies included for qualitative analysis.

ID-Study	Quantitative Analysis	N[a]	Treatment	Ocular Complications	Other	Anti-VEGF Treatment
Baba, 2010 (41)	Yes	12	Bevacizumab	0 (0 %)	n/d	n/d
		12	PDT	0 (0 %)	n/d	
Bandello, 2003 (66)	No	12	PDT	0 (0 %)	n/d	
		13	Untreated	0 (0 %)	n/d	
Bandello, 2013 (62)	No	222	Ranibizumab	2 (0.8 %) SAEs i) corneal erosion 90 (40.4 %) AEs	11 (4.9 %) SAEs i) myocarditis ii) atrial tachycardia iii) lung adeno-carcinoma iv) subdural hematoma 99 (44.3 %) AEs	1+PRN (VA stability versus Disease activity)
		55	PDT	20 (37.7 %) AEs	24 (45.3 %) AEs	
Brancato, 1988 (42)	No	9	Laser (577)	n/d	n/d	
		9	Laser (590)	n/d	n/d	
		9	Laser (620)	n/d	n/d	
Brilliance Study, 2019 (29)	No	182	Ranibizumab	1 (<1 %) retinal detachment	0 (0 %)	2+PRN (Visual Acuity guided)
		184	Ranibizumab	1 (<1 %) retinal detachment	0 (0 %)	1+PRN (Disease guided)
		91	PDT	1 (<1 %) (1 endophthalmitis after switch to ranibizumab)	0 (0 %)	
Calvo-González, 2017 (67)	No	26	Ranibizumab	n/d	n/d	1+PRN
		35	Ranibizumab	n/d	n/d	3+PRN
Cha, 2014 (43)	Yes	23	Ranibizumab	0 (0 %)	0 (0 %)	1+PRN
		43	Bevacizumab	0 (0 %)	0 (0 %)	1+PRN
Chan, 2007 (58)	No	22	PDT + TCA	10 (46 %) IOP increase 3 (20 %) cataract progression	0 (0 %)	
		22	PDT	0 (0 %)	0 (0 %)	
Chen, 2011 (39)	No	17	Bevacizumab	n/d	n/d	n/d
		6	PDT + Bevacizumab	n/d	n/d	n/d
Chen, 2020 (68)	Yes	31	Conbercept	0 (0 %)	0 (0 %)	1+PRN
		33	Ranibizumab	0 (0 %)	0 (0 %)	1+PRN

Costa, 2006 (69)	No	8	PDT (standard 50 J/cm2)	n/d	n/d	
		8	PDT (two-fold 100J/cm2)	n/d	n/d	
Dethorey, 2010 (70)	No	19	Ranibizumab	n/d	n/d	n/d
		34	PDT	n/d	n/d	
El Habbak, 2016 (71)	No	10	Ranibizumab	n/d	n/d	1+PRN
		10	Aflibercept	n/d	n/d	1+PRN
Erden, 2019 (40)	Yes	12	Aflibercept	0 (0 %)	0 (0 %)	1+PRN
		18	Ranibizumab	0 (0 %)	0 (0 %)	1+PRN
Farinha, 2013 (72)	No	11	PDT	n/d	n/d	
		8	Ranibizumab	n/d	n/d	n/d
		9	PDT + Ranibizumab	n/d	n/d	PDT+IVR not simultaneous, patients with PDT switched to IVR if necessary
Fernandez, 2013 (73)	No	8	Ranibizumab	0 (0 %) no serious Aes	0 (0 %) no serious Aes	1+PRN
		8	Bevacizumab	0 (0 %) no serious Aes	0 (0 %) no serious Aes	1+PRN
Fonseca, 2010 (74)	No	25	Bevacizumab	0 (0 %) no serious Aes	0 (0 %) no serious Aes	1+PRN
		19	Ranibizumab	0 (0 %) no serious Aes	0 (0 %) no serious Aes	1+PRN
Freitas-da-Costa, 2014 (65)	No	67 (IVB + IVR)	Bevacizumab	1 (<1 %) sterile vitritis	0 (0 %)	1+PRN
			Ranibizumab	0 (0 %)	0 (0 %)	1+PRN
Gharbiya, 2010 (18)	Yes	16	Ranibizumab	0 (0 %) no major serious Aes	0 (0 %)	1+PRN
		16	Bevacizumab	0 (0 %) no major serious Aes	0 (0 %)	1+PRN

		34	PDT	0 (0 %) no major serious Aes	0 (0 %)	
Glacet-Bernard, 2007 (22)	Yes	32	Translocation	3 (9.3 %) retinal detachment 1 (3 %) macular hole 1 (3 %) macular fold 2 (6 %) transitory diplopia 2 (6 %) diplopia treated with prism 10 (23 %) cataract extraction	0 (0 %)	
		18	Surgical Removal	7 (39 %) CNV recurrence 2 (11 %) retinal detachment 1 (5 %) subretinal haemorrhage	0 (0 %)	
Hamelin, 2002 (23)	No	14	Translocation	2 (14 %) CNV recurrence 2 (14 %) retinal detachment 1 (7 %) hyphaemia 1 (7 %) macular hole 2 (14 %) transient diplopia	0 (0 %)	
		22	PDT	2 (9 %) occlusions of large choroidal vessels	0 (0 %)	
Hayashi, 2008 (75)	Yes	66	Untreated	0 (0 %)	0 (0 %)	
		43	Bevacizumab	0 (0 %)	n/d	n/d
		44	PDT	n/d	n/d	
Hayashi, 2009 (76)	Yes	74	Untreated	n/d	n/d	
		24	Aflibercept	0 (0 %)	0 (0 %)	3+PRN
Howaidy, 2021 (77)	Yes	24	Ranibizumab	0 (0 %)	0 (0 %)	3+PRN
		23	Ranibizumab	0 (0 %)	0 (0 %)	1+PRN
Iacono, 2012 (26)	Yes	25	Bevacizumab	0 (0 %)	0 (0 %)	1+PRN
		15	Bevacizumab	0 (0 %)	0 (0 %)	1+PRN
Iacono, 2017 (78)	Yes	33	Ranibizumab	0 (0 %)	0 (0 %)	1+PRN
		11	Bevacizumab	0 (0 %)	0 (0 %)	1+PRN
Ikuno, 2010 (79)	Yes	20	PDT	1 (5 %)	n/d	1+PRN
		13	Bevacizumab	0 (0 %)	0 (0 %)	1+PRN
Introini, 2012 (80)	Yes	9	Ranibizumab	0 (0 %)	0 (0 %)	1+PRN
		17	Bevacizumab	n/d	n/d	n/d
Kang, 2017 (81)	Yes	20	PDT	n/d	n/d	

Kobayashi, 2000 (37)	No	20	Radiotherapy	1 (5 %) Conjunctival irritation	0 (0 %)	
		19	Untreated	0 (0 %)	0 (0 %)	
Korol, 2020 (36)	Yes	50	Ranibizumab	0 (0 %)	0 (0 %)	2+PRN
		47	Aflibercept	0 (0 %)	0 (0 %)	2+PRN
Lai, 2012 (64)	Yes	22	Bevacizumab	2 (9 %) cataract progression 1 (4.5 %) increase myopic foveoschisis 1 (4.5 %) macular hole 1 (4.5 %) retinal detachment	0 (0 %)	3+PRN
		15	Ranibizumab	1 (7 %) cataract progression 1 (7 %) progression myopic foveoschisis 1 (7 %) cellophane maculopathy 1 (7 %) retinal thinning	0 (0 %)	3+PRN
Li, 2019 (63)	No	26	Ranibizumab	0 (0 %)	0 (0 %)	1+PRN
		24	Ranibizumab	1 (4 %) retinal detachment	0 (0 %)	3+PRN
Matsuo, 2012 (35)	Yes	22	Anti-VEGF	n/d	n/d	1+PRN
		20	PDT	n/d	n/d	
Miki, 2013 (55)	No	37	Anti-VEGF	0 (0 %)	0 (0 %)	1+PRN
		20	PDT	0 (0 %)	0 (0 %)	
		21	Bisphosphonates	0 (0 %)	0 (0 %)	
		22	Untreated	0 (0 %)	0 (0 %)	
Myrror Study, 2015 (38)	No	90	Aflibercept	1 (1 %) SAE macular hole	1 (1 %) thrombo-emblic event	1+PRN
		31	Sham/Placebo	0 (0 %)	0 (0 %)	
Ng, 2015 (50)	No	77	Bevacizumab	n/d	n/d	3+PRN
		16	Bevacizumab	n/d	n/d	1+PRN
Niwa, 2012 (82)	No	13	Bevacizumab	0 (0 %)	0 (0 %)	1+PRN
		19	Bevacizumab	0 (0 %)	0 (0 %)	3+PRN
Pal, 2010 (83)	No	22	Untreated	n/d	n/d	
		8	PDT	n/d	n/d	
		21	Anti-VEGF	n/d	n/d	n/d
Parodi, 2010 (27)	Yes	18	PDT	0 (0 %)	0 (0 %)	
		17	Krypton Laser Photocoagulation	0 (0 %)	0 (0 %)	
		19	Bevacizumab	0 (0 %)	0 (0 %)	1+PRN
Parravano, 2014 (32)	Yes	43	PDT	n/d	n/d	
		42	Ranibizumab	n/d	n/d	1+PRN

Pece, 2015 (33)	Yes	40	Bevacizumab	0 (0 %)	0 (0 %)	1+PRN
		38	Ranibizumab	2 (5 %) mild anterior Tyndall the day after the first injection	0 (0 %)	1+PRN
Radiance Study, 2014 (28)	No	106	Ranibizumab	1 (<1 %) corneal erosion 12 (11.3 %) conjunctival haemorrhage 8 (7.5 %) punctate keratitis 4 (3.7 %) dry eyes 4 (3.7 %) eye pain 3 (2.8 %) injection site haemorrhage 3 (2.8 %) increased IOP 1 (<1 %) cataract (12 months)	0 (0 %)	VA guided
		116	Ranibizumab	1 (<1 %) retinoschisis 12 (10 %) conjunctival haemorrhage 3 (2.5 %) punctate keratitis 2 (1.7 %) dry eyes 4 (3.4 %) eye pain 3 (2.5 %) injection site haemorrhage 7 (6 %) increased IOP 2 (1.7 %) cataracts (12 months)	0 (0 %)	Disease guided
		55	PDT	1 (1.8 %) dry eye 1 (1.8 %) eye pain 1 (1.8 %) cataract (3 months)	0 (0 %)	
Rinaldi, 2017 (34)	Yes	20	PDT	0 (0 %)	0 (0 %)	
		20	PDT + Ranibizumab	0 (0 %)	0 (0 %)	PDT + 1+PRN
		20	Ranibizumab	0 (0 %)	0 (0 %)	3+PRN
Rishi, 2011 (31)	No	11	PDT	0 (0 %)	0 (0 %)	
		3	PDT + TCA	0 (0 %)	0 (0 %)	
		5	PDT + Bevacizumab	0 (0 %)	0 (0 %)	n/d
		4	PDT + Ranibizumab	0 (0 %)	0 (0 %)	n/d
		3	PDT + Ranibizumab (reduced fluence)	0 (0 %)	0 (0 %)	n/d
Rishi, 2016 (30)	Yes	23	PDT	3 (13 %) chorioretinal atrophy	0 (0 %)	
		25	Anti-VEGF	0 (0 %)	0 (0 %)	n/d
		31	PDT + Anti-VEGF	2 (6.5 %) chorioretinal atrophy	0 (0 %)	n/d
Ruiz-Moreno, 2011a (24)	Yes	28	PDT	0 (0 %)	0 (0 %)	
		27	Bevacizumab	0 (0 %)	0 (0 %)	3+PRN
Ruiz-Moreno, 2011b (84)	Yes	19	Bevacizumab	0 (0 %)	0 (0 %)	3+PRN
		20	Bevacizumab	0 (0 %)	0 (0 %)	1+PRN

Ruiz-Moreno, 2012 (85)	No	107	Bevacizumab	n/d	n/d	1+PRN
		32	Bevacizumab	n/d	n/d	3+PRN
Ruiz-Moreno, 2013a (86)	Yes	53	Bevacizumab	2 lens opacities (not attributed to one group)	0 (0 %)	1+ and 3+PRN
		24	Ranibizumab		0 (0 %)	
Ruiz-Moreno, 2013b (87)	Yes	28	PDT	0 (0 %)	0 (0 %)	
		27	Bevacizumab	0 (0 %)	0 (0 %)	3+PRN
Ruiz-Moreno, 2015 (88)	Yes	78	Bevacizumab	2 lens opacities	0 (0 %)	1+ and 3+PRN
		19	Ranibizumab		0 (0 %)	
Saviano, 2014 (89)	Yes	17	PDT + Bevacizumab	0 (0 %)	0 (0 %)	1+PRN + PDT
		17	Bevacizumab	0 (0 %)	0 (0 %)	3+PRN
Sayanagi, 2019 (90)	Yes	12	Ranibizumab	n/d	n/d	1+PRN
		15	Aflibercept	n/d	n/d	1+PRN
VIP-Report 1, 2001 (19)	No	81	PDT	59 (73 %)	59 (73 %)	
		39	Sham/Placebo	27 (69 %)	27 (69 %)	
VIP-Report 3, 2003 (21)	No	81	PDT	n/d	n/d	
		39	Sham/Placebo	n/d	n/d	
Voykov, 2010 (91)	Yes	11	Bevacizumab	0 (0 %)	0 (0 %)	1+PRN
		10	PDT + Bevacizumab	0 (0 %)	0 (0 %)	1+PRN
Wakabayashi, 2009 (56)	Yes	20	Subtenon TCA	3 (15 %) IOP>21 mmHg	0 (0 %)	
		34	Bevacizumab	0 (0 %)	0 (0 %)	n/d
Wakabayashi, 2011 (92)	No	19	Bevacizumab	0 (0 %)	0 (0 %)	1+PRN
		12	Bevacizumab	0 (0 %)	0 (0 %)	3+PRN
Wang, 2018 (93)	Yes	36	Aflibercept	0 (0 %)	0 (0 %)	1+PRN
		42	Bevacizumab	0 (0 %)	0 (0 %)	1+PRN
Woronkowicz, 2018 (94)	No	85	Bevacizumab	n/d	n/d	n/d
		125	Ranibizumab	n/d	n/d	n/d
Yoon, 2010 (95)	Yes	51	PDT	0 (0 %)	0 (0 %)	1+PRN
		63	Anti-VEGF	0 (0 %)	0 (0 %)	1+PRN
		28	PDT + Anti -VEGF	0 (0 %)	0 (0 %)	1+PRN
Yoon, 2012 (96)	Yes	14	Ranibizumab	0 (0 %)	0 (0 %)	1+PRN
		26	Bevacizumab	0 (0 %)	0 (0 %)	1+PRN

Table 3: Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis adapted by Hutton (45)

Section/Topic	Item #	Checklist Item	Reported on Page
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	Title Page and Abstract
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	Introduction
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction
METHODS			
Protocol and Registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); registration and, if available, provide registration information, including registration number.	Methods (Literature search)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	Methods (Literature search, Study eligibility criteria and Study selection)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods (Literature search)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Methods (Literature search)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods (Study eligibility criteria, Study selection, Data extraction, Data analysis) and Figure 1

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods (Data extraction)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods (Data extraction)
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	Data analysis, Figure 2,4,6 and 8
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of individual studies whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Discussio n
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	Methods (Data analysis)
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: *Handling of multigroup trials;* *Selection of variance structure;* *Selection of prior distributions in Bayesian analyses; and Assessment of model fit.*	Methods (Data analysis)
Assessment of inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Methods (Data analysis)
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods (Data analysis) Discussio n
Additional analysis	16	Describe methods of additional analyses if done, indicating which were prespecified. This may include, but not be limited to, the following: Sensitivity or subgroup analyses; Meta-regression analyses; *Alternative formulations of the treatment network; and Use of alternative prior distributions for Bayesian analyses (if applicable).*	Methods (Data analysis)
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results and Figure 1
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Figure 2,4,6 and 8
Summary of network structure	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment	Results

		network, and potential biases reflected by the network structure.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Methods (Data extraction), Table 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Results
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	Table 1 and 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g., placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	Results
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Methods Data analysis and Results
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	Results
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, researchers, and policymakers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	