Systematic Review and Meta-Analysis

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Safety of antivascular endothelial growth factor administration in the ocular anterior segment in pterygium and neovascular glaucoma treatment

Systematic review and meta-analysis

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Abstract

Background: Anti-VEGF agents has been widely used in ocular diseases, but its safety for treating anterior segment disorders, the conclusions are controversial.

Methods: Several major databases, including CENTRAL, MEDLINE, and EMBASE, were searched. Safety data from 18 randomized controlled trials (RCTs) were used to compare anti-VEGF treatment in the ocular anterior segment in pterygium and neovascular glaucoma treatment with placebo/sham treatment for eye diseases. A meta-analysis for adverse events was performed.

Results: Eighteen RCT studies with 955 eyes were included in the meta-analysis. Significant difference in conjunctival disorders (OR: 1.62; 95% CI, 1.01–2.59; $P = .05$) was noted among the included studies, but not in ocular intolerance (odds ratio [OR]: 0.75; 95% CI, 0.34–1.62; $P = .46$), corneal disorders (OR: 0.71; 95% CI, 0.37–1.37; $P = .31$), or the subgroup analysis of conjunctival disorders.

Conclusions: The administration of anti-VEGF agents in the ocular anterior segment for patients with pterygium and glaucoma was tolerable in tolerance and cornea, but was the risk factor of conjunctival disorders. The healing of corneal epithelium may be delayed in patients with primary corneal epithelial defects after anti-VEGF application. However, due to the limited evidence, further research should be performed on the safety of anti-VEGF administration in patients with different corneal disorders.

Abbreviations: anti-VEGF = antivascular endothelial growth factor, CI = confidence intervals, CNV = corneal neovascularization, OR = odds ratios, RCT = randomized controlled trial, VEGF = vascular endothelial growth factor.

Keywords: adverse event, antivascular endothelial growth factor, anti-VEGF, ocular anterior segment, safety

1. Introduction

Vascular endothelial growth factor (VEGF) is a well-established, potent pro-angiogenic growth factor. Blockade of VEGF using anti-VEGF agents has been widely used in clinical settings as an adjunct for treating age-related macular degeneration[1] and diabetic macular edema, as well as anterior segment ocular diseases associated with neovascularization, such as corneal neovascularization (CNV), pterygium, and neovascular glaucoma.[2–4] Although it has been reported that anti-VEGF agent treatment is safe and efficient in patients with retinal diseases, it has also been reported that intravitreal injection of anti-VEGF agents could induce systemic adverse and ocular adverse effects, such as endophthalmitis. With regards to its safety for treating anterior segment disorders, the conclusions are controversial.

To evaluate whether the administration of an anti-VEGF agent for treating anterior segment diseases will lead to a risk of ocular adverse events compared with placebo, we performed a systematic review and meta-analysis of all relevant randomized controlled trials (RCTs).

2. Methods

2.1. Search strategy

A systematic search of the literature (see strategy, Supplemental Digital Content 1, http://links.lww.com/MD/C411, which descripts the full search strategy for the different databases) was performed without restriction to regions, publication types, or languages in databases such as Ovid MEDLINE (1986 to June 1, 2016), EMBASE (1986–2016, June 1), PubMed MEDLINE (1986 to June 1, 2016), and CENTRAL (1986–2016, June 1).

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S-tH and B-sT contributed equally to this work.

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Design of study (S-yZ); conduct of study (S-tH); collection, management, analysis, and interpretation of data (S-tH, B-sT, OX); preparation of the manuscript (S-tH, OX, Y-jY); and review and approval of the manuscript (S-yZ).

The authors have no conflicts of interest to disclose.

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2.2. Inclusion and exclusion criteria

The RCTs had to meet the following criteria to be included in the analysis: ocular diseases were treated with an anti-VEGF agent in the anterior segment; participants were patients who received topical, subconjunctival, or intracameral injection of an anti-VEGF agent compared with a sham or placebo treatment; adverse events were reported; and the study design was a randomized controlled trial in pterygium or glaucoma. The exclusion criteria were as follows: the study results were not published in full, but in abbreviated form such as an abstract; articles reporting the study results contained repeated or similar data; or if multiple studies described the same population, the study with the most detailed outcome was used and the others were excluded.

2.3. Study selection

Two reviewers conducted independent assessments of the research results by analyzing the titles and abstracts and assessing the relevant full-text articles for the final selection. Discrepancies were resolved by consulting a third reviewer (Dr SYZ).

2.4. Data extraction and risk of bias assessment

The 2 reviewers independently extracted the data from the included studies with the same inclusion criteria. Discrepancies were resolved in consultation with the third reviewer. The study characteristics, including the study design, participants, interventions, follow-up time, and complications, were documented. The Cochrane Risk of Bias Tool was used to evaluate bias based on the following: sequence generation and allocation sequence concealment (as selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), funding for the trial, and financial relationship reported by the authors. Discrepancies were resolved by the third reviewer.

2.5. Data synthesis and statistical analysis

IBM SPSS 20.0 software was used to analyze the data collected in this study. A P value less than.05 was defined as significant.

The primary outcome was the proportion of patients who experienced an ocular anterior segment adverse event. Odds ratios [ORs] with 95% confidence intervals (CIs) were calculated to evaluate the safety of treatment. Subgroup analyses based on different medication routes or dosage of the anti-VEGF agent were performed to compare the anti-VEGF group and the control group.

The variability in heterogeneity of the included studies was assessed based on the following characteristics: variability of participants, interventions, outcomes, study design, and risk of bias. In addition, the I^2 value was used to indicate statistical heterogeneity. A value of I^2 lower than 50% was considered low heterogeneity, a value between 50% and 75% was considered moderate heterogeneity, and a value greater than 75% was high heterogeneity. A fixed-effects model was used to assess the studies with low heterogeneity, and a random effects model was used for the other studies.

Evidence quality assessment of this meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis.

3. Results

3.1. Result of search

The process of selection for inclusion of original articles is shown in Fig. 1. The electronic search on June 1, 2016 yielded 1174

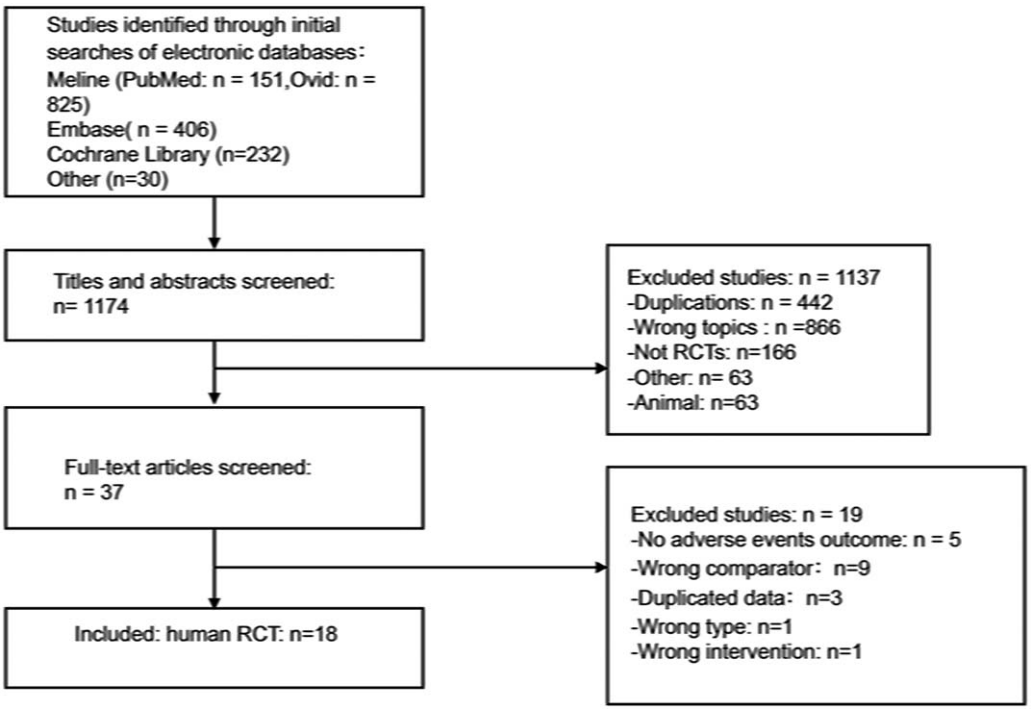

Figure 1. Flowchart of article selection for systematic review and meta-analysis to assess the safety of applying antivascular endothelial growth factor (anti-VEGF) agents in the ocular anterior segment.

relevant titles. After removing 442 duplicates by screening the titles and abstracts, and with further screening by abstract and other standards as listed in Fig. 1, 37 possibly relevant RCTs were further screened using their full texts. A total of 19 articles were excluded for the following reasons: no report of adverse events or details (n,5); no comparison with a sham control or placebo arm (n,9); duplication of data (n,3); only a protocol without any results reported (n,1); and administration of anti-VEGF agent by intravitreal injection (n,1). Three studies reported similar results by 1 study team (Razeghinejad et al,[5] Razeghinejad and Banifatemi,[6] and Banifatemi et al[7]). After evaluating the data, Banifatemi's report (2011) was included as it contained more detailed results. Finally, 18 eligible articles with results[7–25] remained for the meta-analysis.

3.2. Study characteristics

In the 18 included studies, several anti-VEGF agents[7–12,14–25] such as bevacizumab (Avastin), pazopanib, and ranibizumab (Lucentis) were used. The method, timing, indication, and dosage of the anti-VEGF treatment are listed (see table, Supplemental Digital Content 2, http://links.lww.com/MD/C411, which summarizes the numbers of human studies) and detailed information is provided in Table 1. In general, most of the included studies did not record ocular surface conditions before anti-VEGF treatment, or the timing or duration of the adverse events.

3.3. Quality assessment

The risk of bias in the studies analyzed is presented in Fig. 2. The quality of these studies was generally high. For the random sequence generation, 9 studies (50.0%) were considered to have a low risk of bias, and the level of risk for bias was unclear in 7 studies (38.9%). One trial was considered to have a high risk for bias as it used the last digit of the serial number of the patient's medical records to randomize.[18] For allocation concealment, 7 trials (38.9%) were rated as low risk and 9 studies (50.0%) were unclear. For blinding of participants, 8 studies (44.4%) were rated as low risk of bias. For outcomes assessments, 13 trials (72.2%) were considered low risk. However, for incomplete outcome, 2 trials were rated as having a high risk of bias because of the absence of reporting relevant methods for resolving missing data.[22,24] Fifteen of the included articles (83.3%) were rated as low risk for selective reporting. Among 3 trials (16.7%) that reported receiving funding for their research, 2 trials[11,25] were supported by the government and 1 by the pharmaceutical industry.[26] No financial conflicts of interest were declared in 5 trials (27.8%).

3.4. Safety of anti-VEGF administration in the ocular anterior segment

Data were pooled to assess the difference in occurrence of adverse events between administration of anti-VEGF into the ocular anterior segment and sham/ placebo in 955 eyes from 18 studies. No serious systemic adverse events were reported. No any ocular adverse event was reported in either the intervention group or in the control arm in 4 RCTs.[10,14,17,20]

Each adverse event served as 1 unit of analysis. Since repeat adverse events can occur in the same participant, overall adverse events were divided into 4 groups based on the grades assigned by the reviewers: ocular intolerance; conjunctival adverse events; corneal adverse events; or filtering bleb adverse events. In the ocular intolerance group, foreign body sensation, ocular discomfort, and eyelids pruritus were defined as "light discomfort." Eye pain, administration site pain, burning and stinging, and instillation site pain were defined as "ocular pain. " Photophobia, lacrimation, epiphora, and eye irritation were defined as "eye irritation; " and eyelid disorder and blepharospasm were defined as "blepharospasm. " In the conjunctival adverse event group, conjunctival erythema, conjunctival hyperemia, subconjunctival hemorrhage, and light hemorrhage was defined as "conjunctival erythema or subconjunctival hemorrhage. " Graft edema and congestion was defined as "inflammation; " and graft ischemic, pallor of the graft, and flap edema as "conjunctival ischemia. " In the corneal disorder group, corneal epitheliopathy, erosions, punctate keratitis, corneal epithelial staining, and corneal deposits were defined as "corneal epitheliopathy or erosions. "

In the ocular intolerance group, only 3 studies with subconjunctival injections reported eye irritation after the treatment (such as photophobia and lacrimation) as an adverse event. There was no significant difference in the overall effect of ocular intolerance with a low heterogeneity (OR: 0.75; 95% CI, 0.34–1.62; $P=.46$; I^2, 6%) (see figure, Supplemental Digital Content 3, http://links.lww.com/MD/C411, which demonstrates the forest plot for the fixed-effects model to assess the safety of anterior segment administration of anti-VEGF treatment for ocular intolerance events).

For conjunctival adverse events, there was significant difference in the complications associated with conjunctival disorders between the anti-VEGF group and the control group in 9 studies (611 eyes) as shown in Fig. 3 (OR: 1.62; 95% CI, 1.01–2.59; $P=.05$). The adverse events of conjunctival erythema or subconjunctival hemorrhage were reported in 5 studies without a significant difference between the treatment group and the control group (OR: 1.62; 95% CI, 0.71–3.68; $P=.25$). The rate of conjunctival autograft ischemia was only presented in 3 studies with subconjunctival injection treatment.[7,15,21] Scleral flap problems were shown in 1 study during intracameral injection of bevacizumab. There was statistical significance in conjunctival ischaemic adverse events with low heterogeneity (OR: 2.99; 95% CI, 1.24–7.24; $P=.02$; I^2, 66%). In terms of the subgroup analysis, the subtotal pooled OR was 2.27 for topical administration (95% CI, 0.59–8.74; $P=.23$; I^2, 0%) and 1.39 for subconjunctival injection (95% CI, 0.82–2.33; $P=.22$; I^2, 24%). However, the results neither in Supplemental Digital Content 4, http://links.lww.com/MD/C411 nor in Supplemental Digital Content 5, http://links.lww.com/MD/C411 were nonsignificantly different (see figures, Supplemental Digital Content 4, http://links.lww.com/MD/C411, which demonstrates the forest plot for the fixed-effects model to assess the safety of topical treatment of anti-VEGF in the conjunctiva; Supplemental Digital Content 5, http://links.lww.com/MD/C411, which is the forest plot for the fixed-effects model to assess the safety of subconjunctival injection of anti-VEGF for ocular intolerance events).

For corneal adverse events, there was no significant difference between the anti-VEGF and control groups in 5 studies including 312 eyes (OR: 0.71; 95% CI, 0.37–1.37; $P=.31$) (Fig. 4). Epithelial complications such as epithelial erosion and epithelial defect were noted in 1 study. However, epithelial erosion events and corneal edema events were only reported in studies with subconjunctival injection of anti-VEGF. As the limited studies, subgroup analysis of different administration was not carried out.

In the 18 included studies, intracameral injection of anti-VEGF was only applied in 2 studies, in which adverse events were scleral flap problems, vitreous prolapse, choroidal detachment, hypotony, positive Siedel sign, hyphemia, vitreous bleeding, and

Table 1

Detail characteristics and adverse events of included studies.

Reference (First author)	Journal	Blind	Indication	Mean age ± SD (y)	Eye	Surgery	Intervention time	Study group (numbers)	control group (numbers)	Dose	Mean F-U ± SD	Complication in study group (number of eye)	Complication in control group (number of eye)
Banifatemi	J Ocul Pharmacol Ther	DB	Pterygium	44.13 ± 12.27	44	Excision of pterygium + CAT	During surgery, 4 days after surgery	7.5 mg SIB (n = 22)	SIBS (n = 22)	5 mg/0.2 mL, 2.5 mg/0.1 mL	1 m	Corneal epithelial defect (n = NM), Photophobia (n = 5), Lacrimation (n = 7), Conjunctival erythema (n = 9), Conjunctival flap edema (n = 10), Subconjunctival hemorrhage (n = 7)	Corneal epithelial defect (n = NM), Photophobia (n = 2), Lacrimation (n = 8), Conjunctival erythema (n = 7), Conjunctival flap edema (n = 10), Subconjunctival hemorrhage (n = 11)
Nava-Castaneda A	Clin Experiment Ophthalmol	M	Pterygium	48.8 ± 15.5	49	Excision of pterygium + CAT	During surgery, with/without second injection on 15 days after surgery	G1:single SIB (n = 16) G2:double SIB (n = 17)	no injection (n = 16)	2.5 mg/0.1 mL	12 m	Graft ischaemic (G1: n = 6, G2: n = 10)	None
Ozgurhan E B	Cornea	M	Pterygium	48.4 ± 11.3; 48.4 ± 11.3	44	—	1 month after surgery	TB (n = 22)	Artificial tear (n = 22)	5 mg/mL	6 m	Conjunctival cyst (n = 1), Subconjunctival hemorrhage (n = 1)	Conjunctival cyst (n = 1)
Razeghinejad MR	Ophthalmic Research	DB	Pterygium	45.88 ± 16.07, 41.68 ± 13.9	30	Pterygium excision + rotational CAT	During surgery,	1.25 mg SIB (n = 17)	SIBS (n = 21)	1.25 mg/0.1 mL	1 m	Photophobia (n = 2, on the 7th day), Lacrimation (n = 5, on the 7th day)	Photophobia (n = 5, on the 7th day), Lacrimation (n = 5, on the 7th day),
Shahin MM	Ophthalmic Surg Lasers Imaging	M	Pterygium	58.12 ± 4.91	41	Pterygium excision + LCAT	During surgery	SIB (n = 20)	No injection (n = 21)	1.25 mg/0.05 mL	8 m	Conjunctival irritation (n = 3) Pallor of the graft (n = 2) (1 of them lost finally),	Conjunctival irritation (n = 6), Pallor of the graft (n = 0)
Shenasi A	Cornea	DB	Pterygium	58.67 ± 14.60, 55.94 ± 12.68	80	Pterygium excision	During surgery	SIB (n = 33)	Subconjunctival injection of distilled water (n = 33)	1.25 mg/0.1 mL	9 m	Epithelial defect (n = 15), Conjunctival inflammation (n = 14), Pyogenic granuloma (n = 1), Corneal ulcer (n = 1)	Epithelial defect (n = 15), Conjunctival inflammation (n = 14), Dellen formation (n = 3), Pyogenic granuloma (n = 0), Corneal ulcer (n = 0)
Singh P	Indian J Ophthalmol	TB	Pterygium	37.33	60	Excision of pterygium + CAT	1 week before surgery	SIB (n = 30)	SIBS (n = 30)	1.25 mg/0.05 mL	3 m	Subconjunctival hemorrhage (n = 2) Graft edema and congestion (n = 2) Conjunctival cyst (n = 1)	Subconjunctival hemorrhage (n = 2) Graft edema and congestion (n = 1) Conjunctival cyst (n = 1)
Sedghipour MR	Clin Ophthalmol	DB	Glaucoma	67.5	37	Trabeculectomy	During surgery	0.2 mg SIB (n = 17)	SIBS (n = 20)	0.2 mg	3 m	None	None
Saeed A M	Clinical Ophthalmology	NM	Glaucoma	59.53 ± 7.04	28	Trabeculectomy + MMC	During surgery	0.2 mg SIB (n = 14)	No injection (n = 14)		24 m	Conjunctival buttonhole (n = 1) Scleral flap problems (n = 1) Iris prolapse (n = 1) Vitreous prolapse (n = 1) Intrableb bleeding (n = 1) Hypotony (n = 1) Corneal edema (n = 1)	Conjunctival buttonhole (n = 1) Iris prolapse (n = 1) Anterior Chamber bleeding (n = 1) Vitreous prolapse (n = 1) Hypotony (n = 1) astigmatism (n = 2) Serous choroidal detachment (n = 1) Macular edema (n = 2) Hyphema (n = 2) Corneal edema (n = 2) Bleb leak (n = 1) Ischemic avascular cystic bleb (n = 3) Blebitis (n = 1) High bleb with dellen (n = 3) Tenon's cyst (n = 2)

(*continued*)

Table 1

(continued).

Reference (First author)	Journal	Blind	Indication	Mean age ± SD (y)	Eye	Surgery	Intervention time	Study group (numbers)	control group (numbers)	Dose	Mean F-U ± SD	Complication in study group (number of eye)	Complication in control group (number of eye)
Vandewalle, Evelien	Br J Ophthalmol	DM	Glaucoma	69 ± 10	72	Trabeculectomy	During surgery	Intracameral injection of 1.25 mg bevacizumab (n = 36)	Intracameral injection of balanced salt (n = 36)	1.25 mg	12 m	Subconjunctival haemorrhage (n = 4) Choroidal detachment (n = 5) Corneal epitheliopathy or erosions (n = 1) Sterile vitritis (n = 1) Malignant glaucoma (n = 1) Cataract requiring surgery (n = 5)	Scleral flap problems (n = 1) Vitreous prolapse (n = 1) Choroidal detachment (n = 5) Hyphema (n = 3) Vitreous bleeding (n = 1) Corneal epitheliopathy or erosions (n = 4) Cataract requiring surgery (n = 2)
Karalezli A	Int J Ophthalmol	NM	Pterygium	53.04 ± 11.81 58.82 ± 12.02	88	Pterygium excision +LCAT	During surgery,	TB (n = 42)	Topical antibiotics and steroids (n = 46)	5 mg/mL	29.3 ± 4.2 m ,28.5 ± 3.4 m	None	None
Hwang S	Korean J Ophthalmol	DM	Pterygium	73.9 ± 6.7	59	Pterygium excision	After surgery	2.5% TB 4t/d (n = 26)	Artificial tear 4t/d (n = 33)	2.5%	6 m	Subconjunctival hemorrhage (G1: n = 1; G2:n = 1; G3: n = 2)	Subconjunctival hemorrhage (n = 2)
Kasetsuwan N	Clin Ther	DB	Pterygium	50.7, 59.3	22	Pterygium excision	After the completion of epithelialization	0.05% TB (n = 12)	Placebo (n = 10)	0.05%	3 m	Corneal defect (n = 1)	Corneal defect (n = 1)
Kiddee W	J Glaucoma	M	Pterygium	67.2 ± 8.8 65.3 ± 8.5	46	Trabeculectomy + MMC	During surgery	SIB (n = 20)	Sham-treated controls (n = 19)	1.25 mg/0.05 mL	12 m	Encapsulated bleb avascular (n = 4)	Encapsulated bleb (n = 3), Hypotony (n = 1)
Lin YN	International Journal of Ophthalmology (c/o Editorial Office)	—	Pterygium	53.52 ± 6.56 52.44 ± 6.32	66	—	—	Intralesional injection of 1.25 mg bavacizumab (n = 34)	Artificial tear and NSAID eye drop (n = 32)	100 mg/4 mL	6 m	None	None
Tai TY	J Glaucoma	—	Glaucoma	64.6 71.2	58	Needle bleb revision	During surgery	1.0 mg SIB (n = 29)	0.04 mL SIBS (n = 29)	25 mg/mL	6 m	Hyphema (n = 4), Shallow anterior chamber (n = 7), Endothelial folds (n = 4)	Hyphema (n = 3), Shallow anterior chamber (n = 5); Endothelial folds (n = 4)
Fakhraie G	J Glaucoma	DB	Glaucoma	72.19 ± 4.71 73.06 ± 5.40	71	Trabeculectomy	During surgery	Intracameral injection of 1.25 mg bevacizumab (n = 32)	Intracameral injection of 0.05 mL balanced salt solution (n = 33)	25 mg/mL	10.7 ± 2.11 m, 10.5 ± 2.5 m	Encapsulated filtering bleb (n = 8), Filtering bleb leak (n = 11), Clot hyphema (n = 1), Choroidal effusion (n = 3)	Encapsulated filtering bleb (n = 14), Filtering bleb leak (n = 3), Clot hyphema (n = 0), Choroidal effusion (n = 3)
Ozsutcu M	Indian J Ophthalmol	B	Pterygium	42.25 43.25	60	Pterygium excision +rotational CAT	During surgery, 1week after the surgery	SIB (n = 30)	No injection (n = 30)	2.5 mg/0.1 mL	9 m	None	None

Data shown in this table include patient characteristics, intervention, and adverse event in the included studies.

B = blind, CAT = conjunctival autograft transplantation, CNV = corneal neovascular, DB = double blind, DM = double mask, LCAT = limbus-conjunctival autograft transplantation, M = mask, MMC = mitomycin C, NM = not mention, NSAID = nonsteroidal anti-inflammatory drugs, PI = pazopanib instilled, SIB = subconjunctival injection of bevacizumab, SIBS = subconjunctival injection of balanced salt solution, TB = topical bevacizumab.

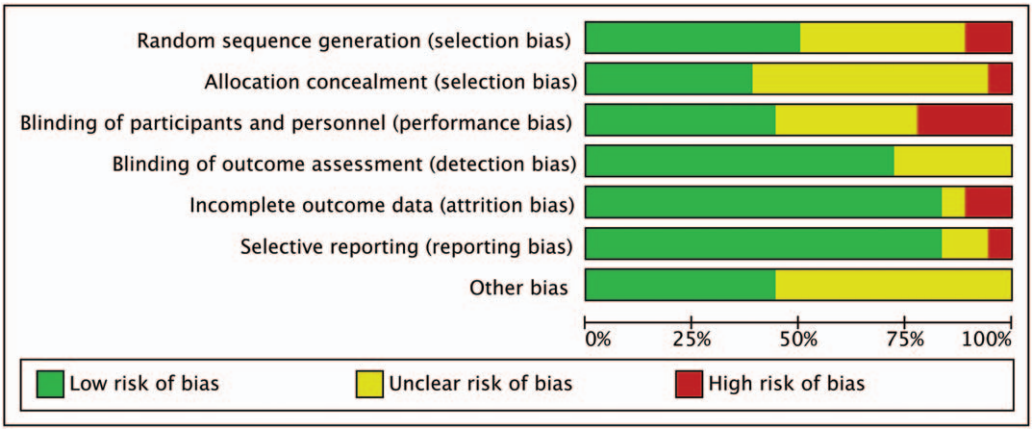

Figure 2. A graph of the risk of bias for each of the included studies.

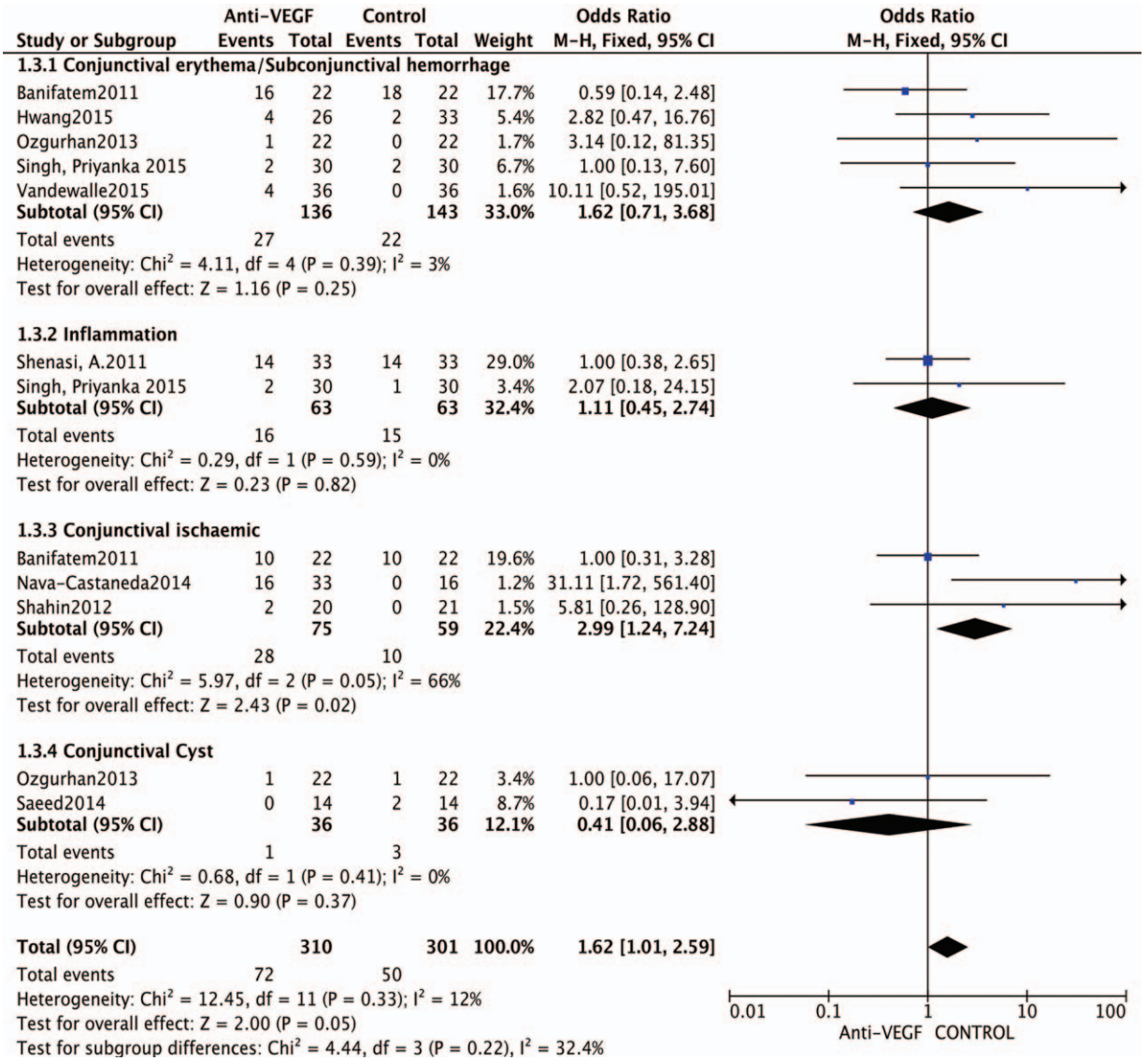

Figure 3. Forest plot for the fix-effects model to assess the safety of anterior segment administration of anti-VEGF treatment in the conjunctiva. Meta-analysis evaluated the odds ratios (ORs) of conjunctival hemorrhage, conjunctival erythema, inflammation, conjunctival ischemia, and conjunctival cyst. The square (sized proportionally to the study weight in the meta-analysis) indicates the OR estimate for each study with lines spanning its 95% confidence interval (CI). VEGF = vascular endothelial growth factor, I^2 = I-squared heterogeneity statistic.

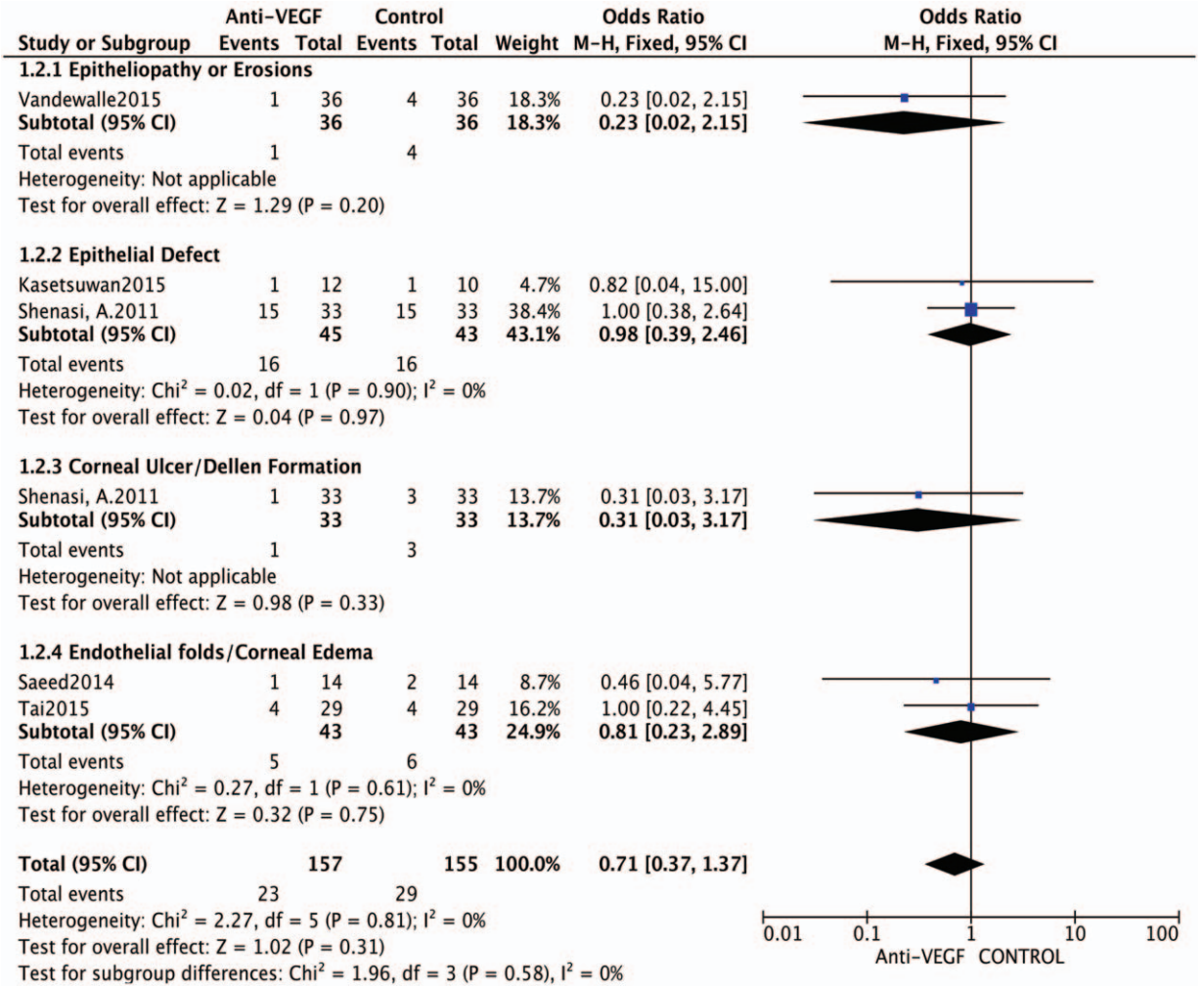

Figure 4. Forest plot for the fixed-effects model to assess the safety of anterior segment use of anti-VEGF treatment in the cornea. Meta-analysis evaluated the odds ratios (ORs) of corneal epitheliopathy or erosion, epithelial defect, corneal ulcer, and endothelial fold. The square (sized proportionally to the study weight in the meta-analysis) indicates the OR estimate for each study with lines spanning its 95% confidence interval (CI). VEGF = vascular endothelial growth factor, I^2 = I-squared heterogeneity statistic.

corneal epitheliopathy/erosions. Given the small number of studies and substantial heterogeneity of adverse events, a subgroup analysis was not performed.

The safety of different dosages of anti-VEGF agent was only investigated in the ocular intolerance and conjunctival adverse event, as the limited studies reported the adverse event in cornea. In our included RCTs, the dosage of anti-VEGF is 5 mg/mL in 2 studies, 12.5 mg/mL in 3 studies, 25 mg/mL in 10 studies, and unclear in the other 3 studies. In the ocular intolerance, all the studies reported the ocular intolerance events administrated 25 mg/mL. Because of the various adverse events in other dosage applications, subgroup analysis of conjunctival adverse event was performed in the studies with 25 mg/mL anti-VEGF. And it is suggested that anti-VEGF group is significantly more possible to get conjunctival adverse event than the control group (OR: 0.91; 95% CI, 1.04–3.52; $P = .04$) (Fig. 5)

4. Discussion

This study included 18 RCTs with 1406 eyes. The pooled results of the studies suggest that use of an anti-VEGF agent in the ocular anterior segment for patients with pterygium and glaucoma is generally safe.

This result was consistent with most of the previous reports suggesting that anterior segment anti-VEGF administration is safe. Hu et al found from their meta-analysis that there were no statistically significant differences in the occurrence of complications between the bevacizumab group and the control group of patients with pterygium, but there was a higher risk of subconjunctival hemorrhage. It is found out that anti-VEGF treatment may be risk factor for conjunctival graft ischemic adverse events in our study. Bahar et al conducted a prospective and consecutive study in 10 eyes with corneal neovascularization due to various diseases. These patients received subconjunctival injection of 2.5 mg/0.1 mL bevacizumab for 2 weeks and no adverse events were observed during the follow-up time of 3.5 months. Likewise, Dastjerdi et al found that treatment with topical bevacizumab 10% for 3 weeks in 10 eyes with stable CNV was well tolerated. Most of the adverse events were conjunctival disorders that may due to the injection procedure. Interestingly, the significant difference was not found out in the subgroup based on administration route, but in the subgroup based on the

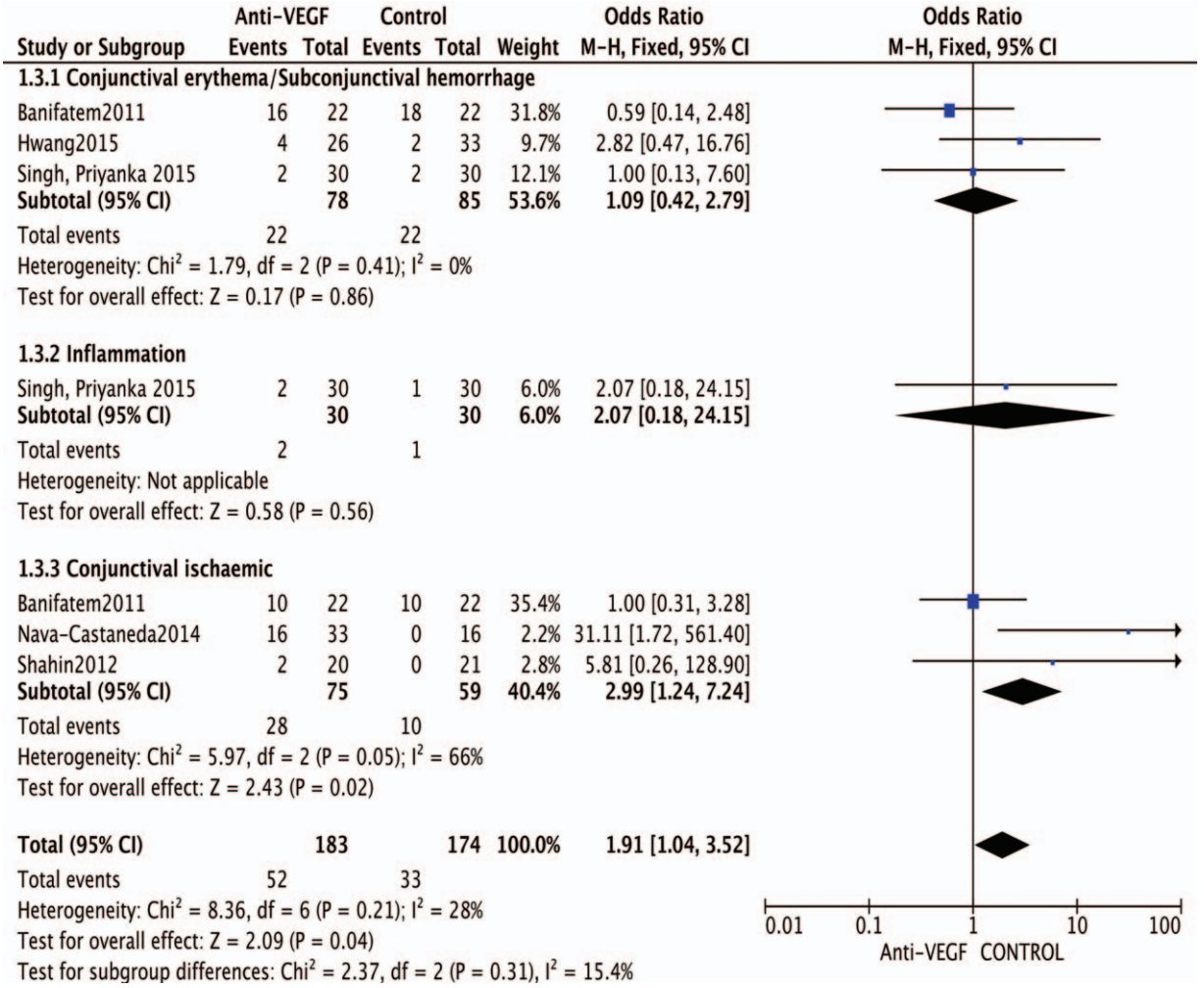

Figure 5. Forest plot for the fixed-effects model to assess the safety of dosage of 25 mg/mL anti-VEGF in the conjunctiva. Meta-analysis evaluated the odds ratios (ORs) of corneal epitheliopathy or erosion, epithelial defect, corneal ulcer, and endothelial fold. The square (sized proportionally to the study weight in the meta-analysis) indicates the OR estimate for each study with lines spanning its 95% confidence interval (CI). VEGF = vascular endothelial growth factor, I^2 = I-squared heterogeneity statistic.

dosage. Subconjunctivally injected bevacizumab more easily to penetrate through an intact epithelium than topically applied bevacizumab.[2] Though, in experimental studies, it was found to be tolerant on cultured human corneal endothelial cell in doses of bevacizumab up to 5 mg,[27] the ideal dosage is still unclear within the limit evidence.

However, as stated before, it was suggested that the healing process for the epithelial defect was slower in anti-VEGF group after pterygium surgery, even though there was no significant difference.[5–7] There are dozens of rodent studies using anti-VEGF agents for various pathologies, but most of them evaluated anti-VEGF effects on CNV, relevant inflammatory factors, or the timing of treatment, and did not report the adverse events. And there were a few studies that reported that the application of anti-VEGF could hinder the healing process in a corneal epithelial defect model.[28–31] Only 1 RCT using anti-VEGF agents for treating corneal neovascular was reported.[32] And there was the epithelia defect event both in the anti-VEGF group and the control group. Kim et al[33] reported a prospective, consecutive, and interventional case series including 10 eyes with CNV that were treated with 1.25% bevacizumab (twice per day) for 3 months. Surprisingly, the anti-VEGF treatment was stopped in 6 eyes in the second month due to delayed side effects, including epithelial defects, stromal thinning, descemetocele, and epithelial erosion. The initial diagnoses for these 6 eyes were severe acid injury, Stevens-Johnson syndrome, and postpenetrating keratoplasty. Koenig et al[34] also found new corneal epithelial defects in 5 eyes (18.5%) after topical bevacizumab treatment (5 mg/mL) for 0.5 to 12 months (5 times/d). These facts suggested that epithelial healing may be postponed in patients with primary corneal epithelial defects, and new corneal epithelial defects may occur after anti-VEGF administration, especially in those with limbal insufficiency. Though our meta-analysis showed no corneal epithelia adverse event was associated with the administration of an anti-VEGF agent, it was likely due to the diverse initial diagnoses, the differing status of the corneal epithelium, and surgical history.

Until now, there was still insufficient evidence to answer whether anti-VEGF administration in the ocular anterior segment is safe or not because of the selection bias of these 18 RCTs in which the corneas were mostly intact before anti-VEGF treatment. Epithelial growth and differentiation are also dynamically regulated by VEGF via various cytokines.[35] Thus, the repair process may be affected by anti-VEGF treatment in

eyes. Bevacizumab is shown to downregulate the expression of nerve growth factor, a polypeptide for promoting corneal epithelium proliferation. Blockade of VEGF could reduce the growth and regeneration of cultured neurons by 17% and 23% in rats.[36] However, as conflicting evidence, bevacizumab did not affect the proliferation of cultured human corneal epithelial cells and was even observed to promote corneal epithelial wound healing.

Among the included studies, only 3 studies reported new corneal defect or ulcer events and the incidence ranged 3% to 8% without a significant difference compared with control group. In another relevant case series, it was pointed out that spontaneous corneal epithelial defects may also be a potential complication of anti-VEGF agent administration to eyes with a history of keratoplasty. Gan et al[37] reported that 4 of 5 eyes developed persistent or recurrent epithelial defects after treatment with an anti-VEGF agent in patients with a history of keratoplasty or limbal transplantation. It was suggested that the adhesiveness of the new corneal epithelium to the underlying extracellular matrix might have been weakened. It was reported that 1.5 mg/mL of bevacizumab could downregulate the expression of surface integrins and collagens in fibroblast cells, and thus delay epithelial closure.[29] Furthermore, the concentrations of epithelial growth factor, basic fibroblast growth factor, insulin-like growth factor-1, and tumor necrosis factor increased in patients treated with bevacizumab and thus might increase corneal susceptibility to complications.[38]

Limitations, such as publication bias, should be taken into account when interpreting the results of this meta-analysis. Few studies mentioned ocular symptoms and the absence of relevant questionnaires also limits the ability to draw a definitive conclusion. Most of these studies did not provide complete information for the adverse events, such as the preoperative ocular condition and the timing of the complication. Also, diverse diseases were included in the 18 RCTs. There were a few small-sized studies that reported severe ocular adverse events after anti-VEGF treatment for CNV after keratoplasty. Unfortunately, most of them were case series and could not be included in this meta-analysis. In addition, the meta-analysis was limited by the categorization of the adverse events, as described in the Methods.

Nevertheless, this meta-analysis showed that the administration of an anti-VEGF agent in the ocular anterior segment for treatment of pterygium and neovascular glaucoma was safe. However, due to the limited evidence, further research should be performed on the safety of different dosage anti-VEGF administration in patients with CNV or keratoplasty. Given the potential risks for corneal epithelial healing in patients with a history of keratoplasty, it is very important to pay more attention to the integrity of the corneal epithelium before administering an anti-VEGF agent into the ocular anterior segment.

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