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Influence of vitreomacular interface on anti-vascular endothelial growth factor treatment outcomes in neovascular age-related macular degeneration

A MOOSE-compliant meta-analysis

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Abstract

The aim of the study was to evaluate the influence of vitreomacular interface configuration on treatment outcomes after intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy for neovascular age-related macular degeneration (AMD).

The Pubmed, Embase, and Cochrane Central Register of Controlled Trials databases were searched to identify relevant prospective or retrospective studies that evaluate the influence of vitreomacular adhesion (VMA) or vitreomacular traction (VMT) on functional and anatomical outcomes in neovascular AMD patients treated with anti-VEGF agents. The outcome measures were the mean change in best corrected visual acuity (BCVA) from baseline, the mean change in central macular thickness (CMT) from baseline, and the mean injection numbers of anti-VEGF treatment from baseline.

In total, 9 studies were selected for this meta-analysis, including 2156 eyes (404 eyes in the VMA/VMT group and 1752 eyes in the non-VMA/VMT group). In neovascular AMD patients treated with anti-VEGF agents, the VMA/VMT group was associated with poorer visual acuity gains and CMT reductions at 1 year (WMD [95% CI], −6.17 [−11.91, −0.43] early treatment diabetic retinopathy study (ETDRS) letters, $P = .04$; WMD [95% CI], 22.19 [2.01, 42.38] μm, $P = .03$, respectively). There was no significant difference between 2 groups in the mean BCVA change and the CMT change over 2 years (WMD [95% CI], −5.59 [−21.19, 10.01] ETDRS letters, $P = .48$; WMD [95% CI], 6.56 [−24.78, 37.90] μm, $P = .68$, respectively). There was no significant difference in the mean injection numbers between 2 groups at 1 year (WMD [95% CI], 0.36 [−0.19, 0.90], $P = .21$), whereas the VMA/VMT group had a significantly higher mean injection numbers over 2 years (WMD [95% CI], 1.14 [0.11, 2.16], $P = .03$).

The limited evidence suggests that vitreomacular interface configuration have a significant influence on the visual acuity gain and CMT reduction at 1 year, injection numbers at 2 years in neovascular AMD patients treated with anti-VEGF agents. However, the results of this meta-analysis should be interpreted with caution because of the heterogeneity among study designs. Eyes with VMA/VMT on optical coherence tomography at baseline may require more intensive treatment with decreased response to anti-VEGF agents.

Abbreviations: AMD = age-related macular degeneration, BCVA = best corrected visual acuity, CI = confidence interval, CMT = central macular thickness, VEGF = vascular endothelial growth factor, VMA = vitreomacular adhesion, VMT = vitreomacular traction, WMD = weighted mean difference.

Keywords: age-related macular degeneration, anti-vascular endothelial growth factor, vitreomacular adhesion, vitreomacular traction

1. Introduction

Anti-vascular endothelial growth factor (anti-VEGF) treatments are effective for the majority of patients with neovascular or wet age-related macular degeneration (AMD).[1] Ranibizumab, bevacizumab, and aflibercept are 3 primary anti-VEGF treatments used in clinical practice today. Several studies validated effective results with these anti-VEGF agents,[2–7] whereas suboptimal or nonresponses remain a challenge.[8] The reasons for nonresponse to anti-VEGF therapies are multifactorial with limited treatment options, which bring blindness, visual impairment, as well as cost implications.[9]

Emerging evidence suggests that vitreomacular interface configuration can adversely affect the prognosis of AMD and visual outcomes after anti-VEGF therapy for neovascular AMD.[10] Vitreomacular adhesion (VMA) and vitreomacular traction (VMT) seems to be more common in eyes with AMD compared to normal controls.[11] Furthermore, there are several studies indicating that VMA or VMT at baseline were associated with poorer functional and anatomical outcomes in neovascular

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AMD patients treated with anti-VEGF agents.[12–16] But whether vitreomacular interface configuration has a significant influence on the efficacy of anti-VEGF agents in neovascular AMD was still a discrepancy.[17–20]

To the best of our knowledge, little study attempted to provide a meta-analysis evaluating the effect of vitreomacular interface configuration on treatment outcomes after anti-VEGF therapy in neovascular AMD. We decided to conduct an independent assessment of the available literature data and to undertake a meta-analysis of all available studies comparing the effect of vitreomacular interface configuration on treatment outcomes after intravitreal anti-VEGF therapy for neovascular AMD.

2. Methods

2.1. Search strategy

The PubMed, Embase, and Cochrane Central Register of Controlled Trials databases were systematically searched without restrictions regarding publication year or language. The following terms were used: vitreomacular adhesion; vitreomacular traction; vitreomacular interface; vitreous detachment; taut posterior hyaloid; age-related macular degeneration; AMD; choroidal neovascularization; ranibizumab; Lucentis; bevacizumab; Avastin; aflibercept; Eylea; antivascular endothelial growth factor; anti-VEGF. A manual search was performed by checking relevant studies cited in selected original reports and review articles. Two reviewers (MG, XDL) conducted the searches independently, and duplicates were excluded. A 3rd reviewer (LML) would resolve disagreements by discussion. The final research was performed on October 2016.

2.2. Inclusion and exclusion criteria

Articles were included in the meta-analysis if the studies met the following inclusion criteria: (1) study design: clinical trial, prospective or retrospective cohort study, or case-control study; (2) population: minimum age of 50 years with neovascular AMD treated with anti-VEGF treatment (bevacizumab, ranibizumab, or aflibercept); (3) intervention: vitreomacular adhesion/vitreomacular traction (VMA/VMT) versus non-VMA/VMT; (4) outcome variables: at least one of the outcomes of interest discussed below was included. Abstracts from conferences and full texts without raw data available for retrieval, duplicate publications, letters, and reviews were excluded. For sequential reports on the same cohort of patients, only the most recent report was included and data that could not be obtained from this last publication were obtained from the previous reports.

2.3. Outcome measures

The outcome measures were the mean change in best corrected visual acuity (BCVA) from baseline, the mean change in central macular thickness (CMT) from baseline, and the mean numbers of anti-VEGF treatment from baseline.

2.4. Data extraction

The data were extracted independently by 2 reviewers (MG, XDL). Disagreements were resolved by discussion and consensus. The information extracted from each study included the authors of each study, the year of publication, location of the trial, information on study design, duration of the study, number of subjects, the anti-VEGF treatment strategy, the mean change in BCVA measured as Early Treatment Diabetic Retinopathy Study letters, the mean change in central macular thickness, and the mean injection numbers of anti-VEGF treatment.

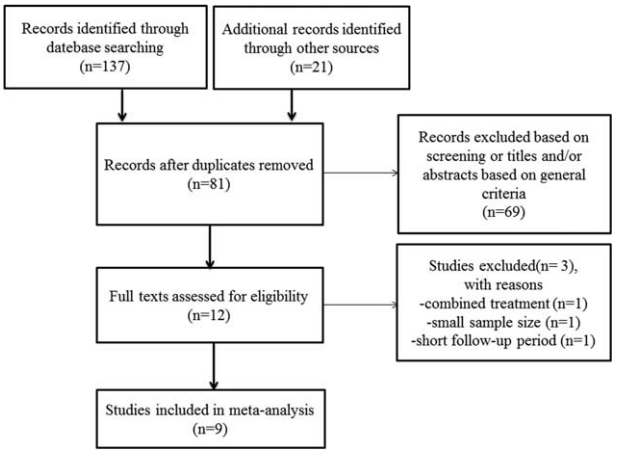

Figure 1. Flow diagram of studies included in this meta-analysis.

2.5. Qualitative assessment

Study quality was independently evaluated by 2 independent observers (MG, YPY) using the Newcastle–Ottawa scales (NOS).[21] The NOS assesses study quality by using the following 3 categories: selection, comparability, and exposure/outcome. The total score ranged from 0 to 9. A study awarded 6 or more stars was defined as a high-quality study in our meta-analysis.

2.6. Statistical analysis

The quantitative data were entered into Cochrane Review Manager (Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The weighted mean difference (WMD) was measured for continuous variable. All outcomes were reported with a 95% confidence interval (CI). $P < .05$ was considered statistically significant on the test for the overall effect. The I^2 statistic was calculated to assess heterogeneity between studies ($P < .05$ was considered representative of significant statistical heterogeneity). If there was heterogeneity between studies, a random-effects model was applied to the data. Alternatively, a fixed-effects model was used for pooling the data. Funnel plot was used to assess publication bias.

2.7. Ethical approval

This is a meta-analysis about literatures; therefore, ethical approval was not necessary.

3. Results

3.1. Literature search

A flow diagram showing how relevant studies were identified is presented in Figure 1. A total of 12 potentially relevant publications were focused on the effects of vitreomacular interface on anti-VEGF treatment for exudative AMD. Among

Table 1

Characteristics and quality scores of included studies.

Author and year	Location	No. eyes(*/†)	Study design	Study group	Control group	Follow-up	Anti-VEGF regimen	NOS score
Krishnan et al[12]	UK	34/29	Retrospective	VMT	Non-VMT	1 year	Ranibizumab, Bevacizumab; loading plus PRN	6
Houston et al[17]	USA	51/153	Retrospective	VMA	Non-VMA	2 year	Ranibizumab, Bevacizumab, Aflibercept; loading plus TER	7
Ciulla et al[18]	USA	143/972	Prospective	VMA or VMT	Neither VMA or VMT	2 years	Ranibizumab, Bevacizumab; monthly or loading plus PRN	8
Nomura et al[13]	Japan	15/108	Retrospective c	VMA	Non-VNA	1 year	Ranibizumab; loading plus PRN	6
Uney et al[14]	Turkey	36/25	Retrospective	VMA	PVD	Mean 22 months	Ranibizumab, Bevacizumab; loading plus PRN	7
Filloy et al[15]	Spain	18/47	Retrospective	VMT	Non-VMT	Mean 21 months	Ranibizumab	6
Mayer-Sponer[19]	Austria	37/162	Prospective	VMA	PVD	1 year	Ranibizumab; monthly or quarterly	7
Green-Simms et al[20]	USA	32/146	Retrospective	VMT	Non-VMT	Mean 2.5 years	Ranibizumab, Bevacizumab; loading plus PRN	7
Lee et al[16]	Korea	38/110	Retrospective	VMA	Non-VMA	Mean 21 months	Ranibizumab, Bevacizumab; loading plus PRN	6

* VMA/VMT group.

† non-VMA/VMT group,

PRN = pro re nata, PVD = posterior vitreous detachment, TER = treat and extend regimen, VMA = vitreomacular adhesion, VMT = vitreomacular traction.

these papers, 1 post hoc analysis was excluded because the anti-VEGF treatment strategy was combined with verteporfin photodynamic therapy,[22] 1 retrospective case series was excluded for a small sample size (n = 7),[23] and 1 prospective case series was excluded for a short follow-up period (6 months).[24] Ultimately, 9 publications were included in the meta-analysis.

3.2. Study characteristics and quality assessment

In total, there were 2156 eyes included in this meta-analysis; 404 eyes were included in the VMA/VMT group and 1752 eyes were included in the non-VMA/VMT group. However, 7 studies were retrospective series,[12–17,20] 1 study was a prospective study,[18] and 1 was a subanalysis of prospective multicenter trial.[19] The characteristics of the studies included and NOS quality scores are summarized in Table 1.

3.3. Meta-analysis

Figure 2 shows the mean change from baseline in BCVA from baseline. Five studies reported results at 1 year from baseline, and 2 studies reported studies over 2 years. The VMA/VMT group was associated with poorer visual acuity gains at 1 year from baseline (WMD [95% CI], −6.17 [−11.91, −0.43] ETDRS letters, $P = .04$). There was no significant difference in the mean BCVA change between 2 groups over 2 year (WMD [95% CI], −5.59 [−21.19, 10.01] ETDRS letters, $P = .48$). Heterogeneity

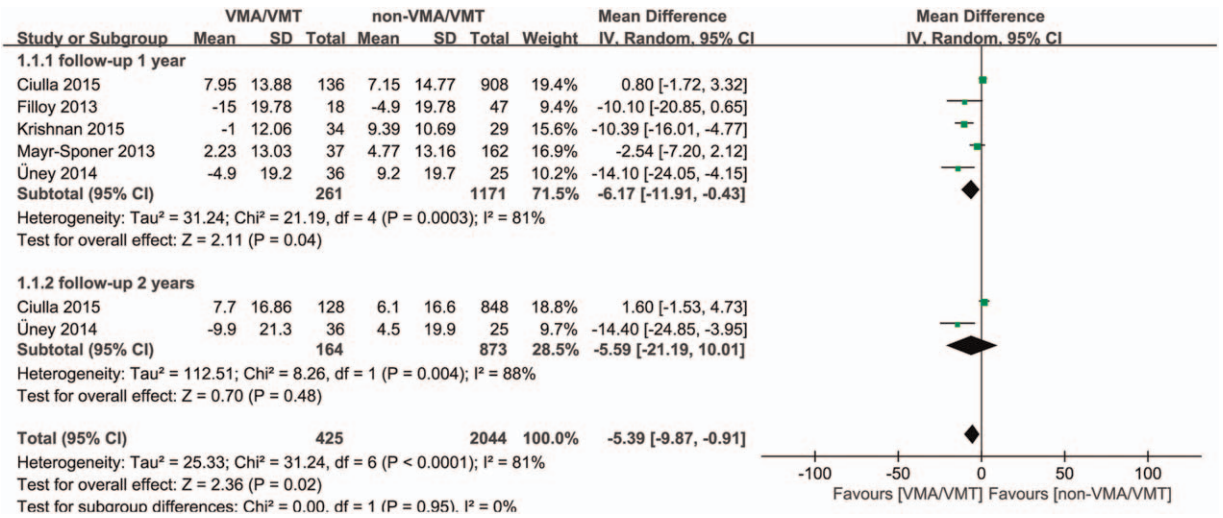

Figure 2. The mean change from baseline in BCVA after intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy for treatment of exudative age-related macular degeneration. The VMA/VMT group was associated with poorer visual acuity gains at 1 year from baseline (WMD [95% CI], −6.17 [−11.91, −0.43] ETDRS letters, $P = .04$). There was no significant difference in the mean BCVA change between the 2 groups at 2 year (WMD [95% CI], −5.59 [−21.19, 10.01] ETDRS letters, $P = .48$). Anti-VEGF = anti-vascular endothelial growth factor, BCVA = best corrected visual acuity, CI = confidence interval, ETDRS = early treatment diabetic retinopathy study, VMA = vitreomacular adhesion, VMT = vitreomacular traction, WMD = weighted mean difference.

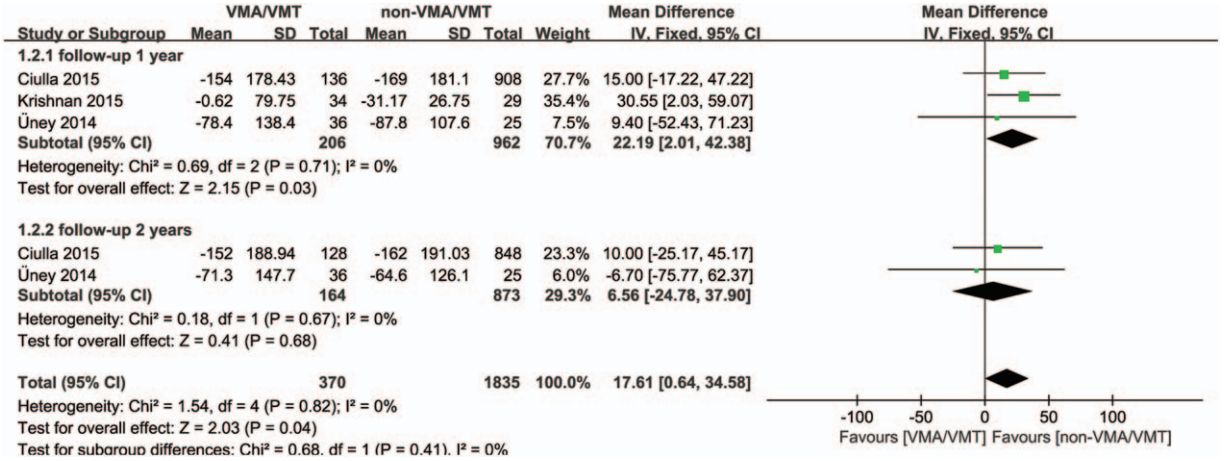

Figure 3. The mean change from baseline in CMT after intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy for treatment of exudative age-related macular degeneration. The mean change in CMT was significantly worse in the VMA/VMT group than that in the non-VMA/VMT group at 1 year from baseline (WMD [95% CI], 22.19 [2.01, 42.38] μm, $P = .03$). There was no significant difference in the mean CMT change between 2 groups at 2 year (WMD [95% CI], 6.56 [−24.78, 37.90] μm, $P = .68$). Anti-VEGF = anti-vascular endothelial growth factor, BCVA = best corrected visual acuity, CI = confidence interval, CMT = central macular thickness, VMA = vitreomacular adhesion, VMT = vitreomacular traction, WMD = weighted mean difference.

among studies was detected respectively ($I^2 = 81\%$; $I^2 = 88\%$), and a random-effects model was applied to the data.

Figure 3 shows the mean change from baseline in CMT from baseline. Three studies reported results at 1 year from baseline, and 2 studies reported studies over 2 years. The mean change in CMT was significantly worse in the VMA/VMT group than that in the non-VMA/VMT group at 1 year from baseline (WMD [95% CI], 22.19 [2.01, 42.38] μm, $P = .03$). There was no significant difference in the mean CMT change between 2 groups over 2 year (WMD [95% CI], 6.56 [−24.78, 37.90] μm, $P = .68$). Heterogeneity among studies was detected respectively ($I^2 = 0\%$; $I^2 = 0\%$), and a fixed-effects model was applied to the data.

Figure 4 shows the mean injection numbers of anti-VEGF treatments from baseline. Six studies reported results at 1 year from baseline, and 6 studies reported studies over 2 years or more. There was no significant difference in the mean injection numbers between 2 groups at 1 year (WMD [95% CI], 0.36 [−0.19, 0.90], $P = .21$), whereas vitreomacular interface configu-

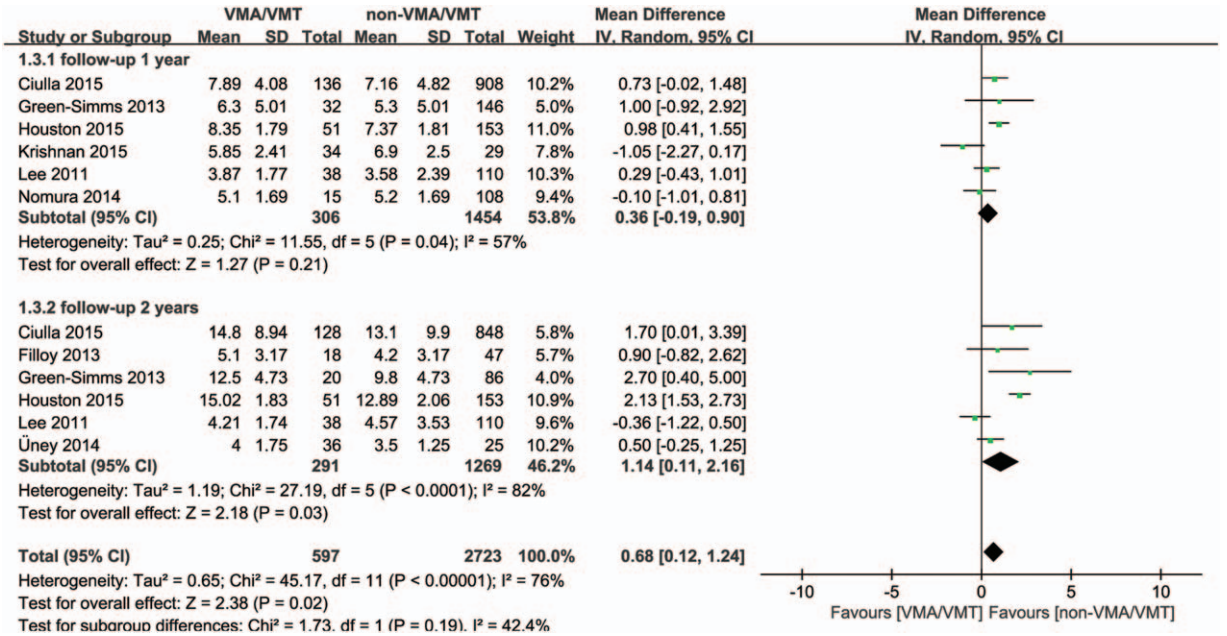

Figure 4. The mean injection numbers from baseline after intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy for treatment of exudative age-related macular degeneration. There was no significant difference in the mean injection numbers between 2 groups at 1 year (WMD [95% CI], 0.36 [−0.19, 0.90], $P = .21$), whereas the vitreomacular interface configuration had a significant influence on the mean injection numbers over 2 years (WMD [95% CI], 1.14 [0.11, 2.16], $P = .03$). Anti-VEGF = anti-vascular endothelial growth factor, BCVA = best corrected visual acuity, CI = confidence interval, VMA = vitreomacular adhesion, VMT = vitreomacular traction, WMD = weighted mean difference.

ration had a significant influence on the mean injection numbers over 2 years (WMD [95% CI], 1.14 [0.11, 2.16], $P = .03$). Heterogeneity among studies was detected respectively ($I^2 = 57\%$; $I^2 = 82\%$).

Publication bias was assessed, but the limited number of involved studies restricted the interpretability of the finding.

4. Discussion

This study investigates whether vitreomacular interface configuration has a significant influence on the functional and anatomical outcomes of anti-VEGF treatments for neovascular AMD patients. The present results show that VMA or VMT at baseline is associated with poorer outcomes on the visual acuity gain and CMT reduction at 1 year, more injection numbers at 2 years in neovascular AMD patients treated with anti-VEGF agents.

The therapeutic response of anti- VEGF agents differs among individuals. A variety of factors could account for poor or nonresponse to anti-VEGF, such as genomic polymorphism and specific genomic risk alleles, lesion characteristics, resistance to anti-VEGF drugs, and vitreomacular structure abnormalities.[9] The precise mechanisms how vitreomacular interface configuration influences the disease progression and treatment outcomes in neovascular AMD patients are still not clear. Vitreomacular adhesion is defined as perifoveal vitreous separation with remaining vitreomacular attachment and unperturbed foveal morphologic features, whereas vitreomacular traction is characterized by anomalous posterior vitreous detachment accompanied by anatomic distortion of the fovea.[25] Despite the differences in definition and pathological progression, VMA and VMT may have a similar influence on retina chronic traction and macular microenvironment.[26,27] VMA or VMT can induce resultant inflammation with mechanical stress, which may aggravate AMD. The mechanical stretching of retina can also induce a high expression of VEGF.[28] Additionally, VMA or VMT was associated with decreased oxygenation, increased VEGF, and other proangiogenic cytokines in front of the macula due to accumulated vitreous cortex.

Currently, 3 anti-VEGF agents are used routinely for the treatment of neovascular AMD (ranibizumab, bevacizumab, and aflibercept). The anti-VEGF treatment regimens in involved studies were mainly monthly dosing and PRN (pro re nata, "as needed") dosing, whereas Houston et al used a TER (treat and extend) regimen. TER regimen consists of initial monthly injections until resolution of exudative activity and then incrementally extending the treatment interval by 1 week to 2 weeks 21. The different anti-VEGF agents and different treatment regimens contribute to a moderate heterogeneity in the meta-analysis of mean injection numbers. Considered the complexity in clinical practice, the study results remain meaningful in assisting clinical decisions.

As a limitation of missing data, only 3 studies are involved in the meta-analysis of mean CMT changes. The present results show the mean change in CMT is significantly worse in the VMA/VMT group than that in the non-VMA/VMT group at 1 year from baseline. Mayer-Sponer et al[19] reported that no influence of the vitreomacular adhesion on CMT could be detected after anti-VEGF treatment, but vitreomacular interface configuration had a significant influence on intraretinal cysts and pigment epithelium detachment reduction, which may be an interesting point for further studies.

There are some limitations in this work. First, the vitreomacular configuration was evaluated at baseline, and limited information can be used to analyze the treatment outcomes by dynamic vitreomacular interface status. Second, a potential source of heterogeneity is the different type of anti-VEGF regimen included in this analysis. The results should be interpreted with caution.

5. Conclusion

In conclusion, based on the limited number of studies available at present, vitreomacular interface configuration has a significant influence on the visual outcomes, CRT reduction and long-term injection numbers in neovascular AMD patients treated with anti-VEGF agents. Eyes with VMA/VMT on optical coherence tomography at baseline may require more intensive treatment with decreased response to anti-VEGF agents.

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