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REVIEW

Real-World Evidence in the Management of Diabetic Macular Edema with Intravitreal Anti-VEGFs in Asia: A Systematic Literature Review

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Purpose: To evaluate the visual outcomes and safety profile of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy in the treatment of diabetic macular edema (DME) in real-world studies in Asian countries.

Methods: A systematic review of electronic literature databases (Embase, Medline, and the Cochrane Library from January 1, 2010, to March 16, 2021) was conducted to identify observational studies that reported clinical and safety outcomes of anti-VEGF treatments for DME in Asia. We analyzed baseline patient characteristics, treatment patterns, mean number of injections, best-corrected visual acuity (BCVA), retinal thickness, and safety outcomes.

Results: Seventy-one studies were included in this review. Most studies reported treatment of DME with ranibizumab (n = 33), followed by aflibercept (n = 13), bevacizumab (n = 28), and conbercept (n = 9). At 12 months, the cumulative mean number of injections for ranibizumab, aflibercept, and conbercept was 5.2, 4.6, and 6, respectively. At the 12-month follow-up, the cumulative mean BCVA gain was 6.8 letters (ranibizumab), 4.6 letters (aflibercept), 4.9 letters (bevacizumab), and 8.3 letters (conbercept). The cumulative mean reduction in retinal thickness at 12 months was 116.9 μm (ranibizumab), 105.9 μm (aflibercept), 81.7 μm (bevacizumab), and 135.2 μm (conbercept). A strong positive correlation (r = 0.78) was observed between mean number of injections and change in BCVA at 12 months. A moderate positive correlation (r = 0.54) was observed between mean number of injections and mean reduction in retinal thickness at 12 months. A weak positive correlation was observed between baseline retinal thickness and visual acuity at 12 months. Baseline BCVA and mean number of injections were predictors of BCVA at 12 months.

Conclusion: All anti-VEGFs were effective in the treatment of DME in Asia. The data suggest that a greater number of anti-VEGF injections was associated with better improvement in BCVA and moderate reduction in retinal thickness at the 1-year follow-up.

Keywords: aflibercept, anti-vascular endothelial growth factors, bevacizumab, conbercept, DME, ranibizumab, retinal thickness, visual acuity

Introduction

Diabetic macular edema (DME), one of the most common causes of vision loss, manifests as retinal thickening caused by alteration of capillary permeability.[1,2] Damage to the retinal microvasculature results in hypoxia, which stimulates the production of vascular endothelial growth factor (VEGF), as well as breakdown of the blood-retina barrier leading to edema.[1,3]

Epidemiological data suggest that approximately 7% of the diabetic patients may be at risk of developing DME and diabetic retinopathy.[4,5] The maintenance of blood glucose levels, lipid levels, and systemic blood pressure is critical in preventing the development and progression of DME.[6] Focal laser photocoagulation therapy was the gold standard for the treatment of patients with DME prior to the advent of intravitreal anti-VEGFs.[7,8] In the Early Treatment Diabetic

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Retinopathy Study (ETDRS), the use of macular laser for clinically significant macular edema reduced the risk of progressive visual loss by approximately 50%.[9] Pharmacological treatment of DME offers the opportunity to reduce central macular thickness (CMT) and results in improvement of visual acuity.[10]

Over the last decade, the introduction of therapeutic agents in the form of intravitreal anti-VEGFs and intravitreal steroids has significantly changed the treatment and prognosis of DME.[11]

Intravitreal anti-VEGFs are presently the first-line treatment option for patients with DME. Other treatment options include the aforementioned intravitreal steroids as well as non-steroidal anti-inflammatory drugs, inhibitors of multiple growth factors, and cytokine and chemokine inhibitors.[7,12] Anti-VEGFs act on the VEGF receptors that mediate the breakdown of the blood-retinal barrier and reverse the vision impairment caused by macular edema[13] and have demonstrated better efficacy compared with laser photocoagulation in several clinical studies.[14–18]

Real-world data on actual treatment patterns and outcomes in daily clinical practice for DME are limited and heterogeneous. The interpretation of this real-world data is essential for understanding how treatments work in clinical settings outside of well-controlled randomized controlled trials. Ethnic and geographical socioeconomic differences are known to affect the real-world efficacy of medical interventions. Thus, the objective of this systematic literature review (SLR) was to collate and report real-world evidence related to the clinical effectiveness and safety and treatment patterns of anti-VEGFs in DME patients in Asian countries.

Methods

Literature Search Strategy and Selection Criteria

This review was conducted by following the systematic principles of the Cochrane Handbook for Systematic Reviews of Interventions[19] and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[20]

Comprehensive literature searches were performed in Embase, Medline, and the Cochrane Library from January 1, 2010, to March 16, 2021, to identify relevant real-world studies. The search term strategy included both medical subject headings (MeSH) and free-text terms related to DME and anti-VEGFs. The detailed search strategy is presented in Table S1–S3.

In addition, conference abstracts (Annual Meeting of Japanese Ophthalmological Society, International Congress of Ophthalmology and Optometry China, the Asia-Pacific Academy of Ophthalmology Congress, ISPOR Asia Pacific, Annual Meeting of The Korean Ophthalmological Society, Asia-Pacific Vitreo-retina Society, the Royal Australian and New Zealand College of Ophthalmologists, and American Academy of Ophthalmology) were hand searched from publication years 2018 to June 2021 to retrieve the latest unpublished studies in journals as well as full-text articles or supplement results of previously published studies.

Based on the predefined eligibility criteria (Table S4), titles and abstracts of all retrieved citations were screened for inclusion. Publications were included in the full-text review if they reported the clinical efficacy, safety, and treatment pattern of anti-VEGFs. Two independent reviewers were involved in the study selection process, and any discrepancies between them were reconciled by a third independent reviewer.

Data Collection and Synthesis

Study characteristics, baseline patient data, and outcomes data were collected. Data from the studies were extracted to a data extraction sheet by 1 reviewer, and quality check was performed by a second independent reviewer, with reconciliation of any discrepancies by a third independent reviewer.

The following outcomes were analyzed to support the objectives of this review: visual acuity (mean change from baseline and the proportion of patients gaining ≥10 letters or losing ≤10 letters), retinal thickness (change from baseline), injection frequency, presence or absence of retinal fluid, number of clinic visits, tolerability, switching, and safety of anti-VEGFs. Patients receiving monthly anti-VEGF injections for at least initial 3 consecutive months were classified into the loading group. Patients receiving <3 injections in the first 3 months were classified into the no loading group.

A qualitative descriptive analysis of these data, including cumulative means (mean of the means of several studies), was used to analyze the data with respect to baseline characteristics and respective outcomes. Mean and cumulative mean

values are reported as mean±standard deviation (SD). A correlation analysis between injection frequency and BCVA/retinal thickness outcomes at 12 months was performed using the Pearson correlation (r). The association of baseline predictors (BCVA and central retinal thickness [CRT]) and mean number of injections at 12 months with change in the BCVA letter score at 12 months was analyzed using the multiple linear regression method.

For the purpose of analysis, the logarithm of the minimum angle of resolution (LogMAR) values were converted to ETDRS letters per the equation "ETDRS letters = 85–50LogMAR" based on the publication by Gregori et al.[21] Subgroup analysis included eyes stratified by baseline BCVA of <69 (worse vision) and ≥69 letters (better vision) based on the Diabetic Retinopathy Clinical Research Network (DRCR.net) protocol.[22] An additional subgroup analysis was performed to compare visual outcomes according to patient history of treatments with anti-VEGFs (naive vs pretreated/mixed treatment patients). Of the studies investigating the efficacy of anti-VEGFs, those with a follow-up of ≥12 months were included in the efficacy analysis.

Results

The literature search yielded 2775 citations, of which 168 were removed as duplicates. Screening of the titles and abstracts of all retrieved citations resulted in 366 potentially relevant references for inclusion. Of these, 75 publications (including 10 conference abstracts) were included in the present review following a detailed examination against the predefined eligibility criteria. Of these 75 publications, 71 were unique studies and 4 were linked to primary studies (Figure S1).

Study Characteristics

The study characteristics including study design, follow-up period, country, intervention, sample size, and outcomes are presented in Table S5. Of the 71 studies included, 65 were retrospective studies and 6 were prospective studies. Sixty-one studies reported data for a single treatment arm, 8 studies reported data for 2 treatment arms, and 2 studies reported data for 3 treatment arms. The studies were mostly conducted in Japan (18), followed by South Korea (15), Taiwan (14), China (12), India (4), Thailand (3), Australia (1), Malaysia (1), New Zealand (1), Pakistan (1), and Singapore (1). The time point of interest for the clinical outcomes (BCVA and retinal thickness) was 12 months. The mean follow-up period in these studies ranged from 0.5[23] to 60[24] months.

Clinical Characteristics of the Study Population at Baseline

The mean (±SD) age of the patients ranged from 52.6 (±14)[25] to 73.9 (±10)[23] years. The size of the study population varied widely, ranging from 14[26] to 2049[27] eyes. At baseline, the duration of DME ranged between 2.6[28] and 27.2[29] months, with the mean±SD duration in all studies being 14.85±8.43 months. The mean baseline BCVA ranged from 39[30] to 72[31] ETDRS letters. The mean baseline CRT ranged from 300.8[32] to 575.9[33] μm.

A total of 27 studies did not report details of naive status (whether patients received prior anti-VEGF therapy). Of the 44 studies that reported details of previous treatment, 31 included only anti–VEGF-naive patients, 3 included only patients who were previously treated with anti-VEGFs, and 11 included both naive and previously treated patients (mixed treatment patients).

Treatment Pattern, Regimen, and Mean Number of Injections

Treatment Pattern

Overall, 33 studies evaluated the use of ranibizumab as a treatment option for DME, followed by 13 on aflibercept, 28 on bevacizumab, and 9 on conbercept (Figure S2A).

In Japan, the use of ranibizumab and aflibercept was common for DME. In Taiwan, ranibizumab was the most prescribed anti-VEGF medication for DME. Off-label bevacizumab was used predominantly in South Korea, whereas conbercept was used only in China (Figure S2B).

Treatment Regimen

Of the 71 studies, 28 reported the practice of administering anti-VEGF loading doses, ie, ≥3 monthly injections. In 13 studies, no information was available on the type of regimen used for anti-VEGFs. The remaining 30 studies reported the

use of either a single injection or a single injection followed by an as-needed approach. Of the 28 studies reporting the use of loading doses, only 1 study[34] reported the use of 5 monthly loading doses for aflibercept and ranibizumab, whereas the remaining 27 studies reported 3 monthly loading doses (3q4w) of anti-VEGF injections. Of the 30 studies with no loading dose, 17 included only treatment-naive patients, 2 included only previously treated patients, and 4 included both naive and previously treated patients (Table 1). Loading doses were reported in 65% of ranibizumab studies, 50% of aflibercept studies, 37.5% of conbercept studies, and 33.3% of bevacizumab studies (Figure S3). Details of the treatment regimen with respect to loading and no loading doses are provided in Table 1.

Mean Number of Injections

Twenty studies reported injection frequency data at 12 months. The mean number of injections in 12 months ranged from 2.9[35] to 7.2,[36] with the cumulative mean being 5.2. The cumulative mean number of injections was higher in studies with naive patients (8 studies, cumulative mean: 5.97; mean number of injections ranged from 3.9[37] to 7.2[36]) than in studies with mixed treatment patients (9 studies, cumulative mean: 4.67; mean number of injections ranged from 3.8[38] to 6.4[39]). Two studies did not report data on prior treatment status (cumulative mean: 4.17; mean number of injections ranged from 2.9[35] to 5[40]). The mean number of injections data at 12 months is not available for studies that included patients who were previously treated with anti-VEGFs (Table 2).

For ranibizumab, 11 studies reported injection frequency at the 12-month follow-up (range: 3.9[37] to 7.2[36]). The cumulative mean number of injections was 5.2 (11 studies with 12 treatment arms). The mean number of injections for ranibizumab 1 dose at baseline (RAN 1q4w) followed by an as-needed approach (pro re nata [PRN]) ranged from 3.9[37] to 4.4,[29] and the mean number of injections for ranibizumab 3q4w (RAN 3q4w) followed by PRN regimen ranged from 4.3[41] to 7.2.[36] Only 1 study reported the mean number of injections for RAN 3q4w followed by treat and extend (T&E) regimen (7.1)[42] at the 12-month follow-up (Figure S4).

Table 1 Number of Studies with Loading and No Loading Doses with Respect to Treatment Regimen

Treatment Regimen	Ranibizumab	Aflibercept	Bevacizumab	Conbercept
Studies with loading dose (N=28; 15 naive, 8 mixed, 6 unclear, 2 prior treated)				
3q4w (N=7)	1 (naive)	1 (previously treated)	4 (3 naive and 1 mixed)	1 (naive)
3q4w PRN (N=19)	14 (7 naive, 7 mixed, 1 previously treated and 1 unclear)	1 (unclear)	2 (1 naive and 1 unclear)	2 (naive)
3q4w T&E (N=3)	1 (naive)	1 (naive)	1 (unclear)	0
5q4w PRN (N=2)	1 (unclear)	1 (unclear)	0	0
3 q4-6w->PRN (N=1)	0	0	1 (unclear)	0
Total number of studies	**17**	**4**	**8**	**3**
Studies with no loading dose (N=30; 17 naive, 11 unclear, 4 mixed, 2 prior treated)				
Single injection (N=12)	2 (1 mixed, 1 unclear)	2 (1 mixed, 1 unclear)	8 (5 naive, 2 unclear, 1 mixed)	0
1q4w PRN (N=21)	7 (5 naive, 3 mixed, 2 previously treated)	2 (unclear)	7 (3 naive, 4 unclear)	5 (3 naive, two unclear)
Total number of studies	**9**	**4**	**15**	**5**

Notes: Data reported for number of studies is not mutually exclusive, because some studies reported data for more than one anti-VEGF and one study (Hayashi 2021[35]) reported data for both loading and no loading regimen.

Abbreviations: 3q4w, 3 monthly doses; 3q4w PRN, 3 monthly doses followed by pro re nata; 3q4w T&E, 3 monthly doses followed by treat and extend; 5q4w PRN, 5 monthly doses followed by pro re nata; 3 q4-6w->PRN, 3 doses 4 to 6 weeks followed by pro re nata; 1q4w PRN, 1 monthly dose followed by pro re nata; VEGF, vascular endothelial growth factor.

Table 2 Number of Studies with Mean Number of Injections Data at 12 Months Based on Prior Treatment Status

Anti-VEGF Received	Naive	Mixed*	Unclear	Previously Treated with Anti-VEGFs
Ranibizumab	5	6	0	0
Aflibercept	1	2	1	0
Bevacizumab	1	0	1	0
Conbercept	4	1	0	0
Total number of studies	**11**	**9**	**2**	**0**

Notes: *Mixed treatment studies (studies with both naive and patients previously treated with anti-VEGFs).
Abbreviation: VEGF, vascular endothelial growth factor.

For aflibercept, 4 studies reported injection frequency at the 12-month follow-up (range: 2.9[35] to 6.5[42]). The cumulative mean number of injections was 4.6 (4 studies with 5 treatment arms). One study each reported mean number of injections for aflibercept 1 dose at baseline (AFL 1q4w) followed by PRN regimen (2.9),[35] aflibercept 3 monthly doses (AFL 3q4w) followed by T&E regimen (6.5),[42] and AFL 3q4w followed by PRN regimen (4.6)[35] (Figure S5).

Two studies reported injection frequency at the 12-month follow-up for bevacizumab. Sepehr et al reported a mean of 5 injections (treatment regimen not specified),[40] and Choovuthayakorn et al reported the use of BEV 3q4w followed by PRN regimen with a median of 6 injections.[43]

Five studies reported injection frequency at the 12-month follow-up for conbercept (range: 4.5[44] to 6.8[45]). The cumulative mean number of injections was 6 (5 studies with 5 treatment arms). Two studies each reported the mean number of injections for conbercept 1 dose at baseline (1q4w) followed by PRN regimen (5.6[46] and 6.8[45]) and conbercept 3q4w followed by PRN regimen (6.6[36] and 6.6[47]) (Figure S6).

Efficacy Outcomes

The efficacy outcomes are summarized in Table S6. On an average, BCVA and retinal thickness parameters were reported for up to 12 months in 25 studies, while 8 studies reported data beyond the 12-month follow-up.

Visual Acuity Outcomes

Mean Change in BCVA from Baseline (ETDRS Letters) at 12 Months

Overall, 42 studies reported change in mean BCVA from baseline at various time points (Figure S7). Mean BCVA values were reported in 41 studies at baseline. In the 22 studies reporting data at 12 months, the mean BCVA ETDRS letters ranged from 46[48] to 72[31] at baseline and 51.4[41] to 74.2[37] at 12 months. The cumulative mean±SD gain in BCVA ETDRS letters with anti-VEGFs was 6.5±2.9 (cumulative mean±SD injections: 5.1±1.2). The cumulative mean gain with conbercept (8.3 ETDRS letters)[36,44–47] and ranibizumab (6.8 ETDRS letters)[29,31,36,37,39,41,48–52] showed greater BCVA improvement than that with aflibercept (4.6 ETDRS letters)[35,38,53] and bevacizumab (4.9 ETDRS letters).[40,43,54] In the subgroup analysis stratified by prior treatment status, studies with naive patients reported higher BCVA letter gain (8.5; mean number of injections: 6.0) than those with mixed treatment patients (5.8; mean number of injections: 4.6) (Table 3).

Two studies reported subgroup data for patients with worse baseline BCVA (<69 ETDRS letters or 20/50 or worse Snellen equivalent) and better baseline BCVA (≥69 ETDRS letters or 20/32–20/40 Snellen equivalent) at the 12-month follow-up. Choovuthayakorn et al included naive patients and reported a significant BCVA letter gain with bevacizumab in the worse baseline BCVA group (mean gain: 8.4; 95% confidence interval [CI] 6.3 to 10.6; median injections: 6; $p < 0.001$) than in the better baseline BCVA group (mean BCVA gain: 2.0 letters; 95% CI −1.6 to 5.6; median injections: 6).[43] Similarly, Li et al reported better BCVA gain with conbercept in the worse baseline BCVA group (median BCVA gain: 18 letters; mean injections: 6.7) than in the better baseline BCVA group (median BCVA gain: 7 letters; mean injections: 6.5)[55] in patients with unclear prior treatment status.

Table 3 Studies with Visual Activity Outcomes at 12 Months

Study Details (Author and Year)	Intervention	Prior Treatment Status to Anti-VEGFs	Baseline BCVA (ETDRS Letters)	BCVA at 12 Months (ETDRS Letters)	Change from Baseline to 12 Months, BCVA Gain (ETDRS Letters)	Mean No. of Injections
Lai 2020b[48]	Ranibizumab	Mixed	46	53.5	7.5	5
Tsai 2019[41]	Ranibizumab	Mixed	46.5	51.4	4.9	4.3
Xu 2017[36]	Ranibizumab	Naive	46.6	55.5	8.9	7.2
Lai 2019[50]	Ranibizumab	Mixed	48	53	5	4.36
Sheu 2018[29]	Ranibizumab	Mixed	48.3	55.5	7.2	4.43
Lai 2020a[49]	Ranibizumab*	Naive	48.5	54.3	5.8	4.6
Lai 2020a[49]	Ranibizumab#	Naive	51.3	66.1	14.8	6.5
Seo 2016[52]	Ranibizumab	Mixed	60	67.5	7.5	–
Murakami 2018[51]	Ranibizumab	Mixed	65.8	73.7	7.9	–
Yoshitake 2020[39]	Ranibizumab	Mixed	67.4	73.5	6.1	6.4
Nagai 2020[37]	Ranibizumab	Naive	70.7	74.2	3.5	3.9
Sato 2017[31]	Ranibizumab	Mixed	72	74	2	4.1
Cumulative mean for Ranibizumab: 11 studies (12 treatment arms), Mean±SD			**55.9±10.4**	**62.7±9.6**	**6.8±3.2**	**5.1±1.2**
Yi-Sheng 2019[53]	Aflibercept	Unclear	47	52	5	5.2
Hayashi 2021[35]	Aflibercept 1q4w PRN	Unclear	64	66	2	4.6
Hayashi 2021[35]	Aflibercept 3 q4w PRN	Unclear	62.5	69.5	7	2.9
Kaiho 2017[38]	Aflibercept	Mixed	65.5	70	4.5	3.8
Cumulative mean for Aflibercept: 3 studies (4 treatment arms), Mean±SD			**59.8±8.6**	**64.4±8.4**	**4.6±2.1**	**4.1±1**
Choovuthayakorn 2020[43]	Bevacizumab	Naive	50.2	57	6.8	–
Sepehr 2019[40]	Bevacizumab	Unclear	66	70	4	5
Lee 2019[54]	Bevacizumab	Unclear	68	72	4	–
Cumulative mean for Bevacizumab: 3 studies, Mean±SD			**61.4±9.8**	**66.3±8.1**	**4.9±1.6**	**5**
Xu 2016[46]	Conbercept	Naive	48.8	57.9	9.1	5.6
Xu 2017[36]	Conbercept	Naive	49.4	58.7	9.3	6.6
Zhou 2019[44]	Conbercept	Mixed	49.5	54	4.5	4.5
Yu 2020[45]	Conbercept	Naive	57.1	67.1	10	6.8
Xu 2019[47]	Conbercept	Naive	57.5	66.2	8.7	6.6

(*Continued*)

Table 3 (Continued).

Study Details (Author and Year)	Intervention	Prior Treatment Status to Anti-VEGFs	Baseline BCVA (ETDRS Letters)	BCVA at 12 Months (ETDRS Letters)	Change from Baseline to 12 Months, BCVA Gain (ETDRS Letters)	Mean No. of Injections
Cumulative mean for Conbercept: 5 studies, Mean ±SD			**52.5±4.4**	**60.8±5.7**	**8.3±2.2**	**6±1**
Cumulative mean for all anti-VEGFs: 21 studies (24 treatment arms), Mean±SD			**56.5±9**	**63.±8.2**	**6.5±2.9**	**5.1±1.2**

Notes: * Before Policy Change (reimbursement up to 5 injections); # After Policy Change (reimbursement up to 8 injections).
Abbreviations: BCVA, best-corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; SD, standard deviation; VEGF, vascular endothelial growth factor.

Ranibizumab. Eleven studies reported change in BCVA from baseline. The mean gain in ETDRS letters ranged from 2.4 letters (baseline: 72; at 12 months: 74.4)[31] to 14.8 letters (baseline: 51.3; at 12 months: 66.1)[31] The highest letter gain (14.8 ETDRS letters) was observed in the RAN 3q4w followed by PRN regimen group with 6.5 mean injections in naive DME patients.[49] In the subgroup analysis stratified by prior treatment status, the mean±SD change in the BCVA letter score from baseline to 1 year was 8.3±4.9 in studies with naive patients[36,37,49] and 6.1±1.9 in studies with mixed treatment patients[29,31,39,41,48,50–52] (Figure S8).

Aflibercept. Three studies reported change in BCVA from baseline. The mean gain in ETDRS letters ranged from 2 letters (baseline: 64; at 12 months: 66)[35] to 7 letters (baseline: 62.5; at 12 months: 69.5).[35] AFL 3q4w followed by PRN regimen with 4.6 mean injections reported the highest letter gain (7 ETDRS letters)[35] (Figure S9). At 12 months, data for naive patients were not available, and only 1 study reported data for mixed treatment patients (mean BCVA gain: 4.5; mean injections: 3.8).[38]

Bevacizumab. Three studies reported change in BCVA from baseline. Mean gain in ETDRS letters ranged from 4 letters (baseline: 66; at 12 months: 70)[40,54] to 6.8 letters (baseline: 50.2; at 12 months: 57).[43] At 12 months, only 1 study reported data for naive patients (mean BCVA gain: 6.8; mean injections: data not available),[43] and data were not available for mixed treatment patients.

Conbercept. Five studies reported change in BCVA from baseline. The mean gain in ETDRS letters ranged from 4.5 letters (baseline: 49.5; at 12 months: 54)[44] to 10 letters (baseline: 57.1; at 12 months: 67.1).[45] Conbercept 1q4w followed by PRN regimen with 6.8 mean injections reported the highest letter gain (10 ETDRS letters).[45] In the subgroup analysis stratified by naive status, the cumulative mean±SD gain in the BCVA letter score from baseline to 1 year was 9.3±0.5 (cumulative mean±SD injections: 6.4±0.5) in studies with naive patients[36,45–47,56] and 4.5 (mean injections: 4.5) in those with mixed treatment patients[44] (Figure S10).

Proportion of Patients with Change in ETDRS Letters (Gain and Loss) at 12 Months

Six studies reported proportion of patients with ≥10 ETDRS letter gain.[29,36,43,46,49,53] Four studies included naive patients, 1 study[29] included mixed treatment patients, and prior treatment status was unclear in 1 study.[53] Among naive patients, the proportion of patients who gained ≥10 ETDRS letters was high (65.9%)[49] in patients treated with RAN 3q4w followed by PRN regimen (mean injections: 6.5) compared with those treated with bevacizumab 3q4w followed by PRN regimen (43.1%; median injections: 6)[43] and conbercept 3q4w followed by PRN regimen (41.7%; mean injections: 6.6).[36] For no loading dose regimens, the proportions of patients who gained ≥10 ETDRS letters were 45.2% and 40% for conbercept 1q4w followed by PRN (mean injections: 5.6)[46] and RAN 1q4w followed by PRN regimen (mean injections: 4.4),[29] respectively. In a study with aflibercept (mean injections: 5.2), 25% of patients gained ≥10 ETDRS letters and regimen details were unclear[36] (Figure S11).

Only 3 studies reported data on the proportion of patients who gained ≥15 ETDRS letters. All these studies included patients naive to anti-VEGFs. At 12 months, the proportion of patients who gained ≥15 ETDRS letters was high (35.8%)[43] in naive patients treated with bevacizumab 3q4w followed by PRN regimen (median injections: 6) compared

with those treated with conbercept 3q4w followed by PRN regimen (19.4%; mean injections: 6.6)[36] and RAN 3q4w followed by PRN regimen (15.6%; mean injections: 7.2)[36] (Figure S12).

Limited evidence was available for the proportion of patients with letters lost after treatment. Naive patients treated with bevacizumab 3q4w followed by PRN regimen (median number of injections: 6) reported loss of ≥10 letters (13.8%) and loss of ≥15 letters (8.1%) at 12 months.[43] In a study conducted in Taiwan, treatment-naive patients were assessed based on before (a maximum of 5 ranibizumab injections were reimbursed for each eye during the first year) and after the major reimbursement policy change (a maximum of 8 ranibizumab injections were reimbursed for each eye during the same period). The proportion of patients with loss of ≥10 letters was 15.9% before the policy change (mean injections: 4.6) and 4.8% after the policy change (mean injections: 6.5). This study used the RAN 3q4w followed by PRN regimen.[49] None of the studies with aflibercept reported data for gain/loss of ≥15 letters at 12 months.

Correlation Between Injection Frequency and BCVA at 12 Months

Overall, 17 studies reported data on the mean number of injections and BCVA gain. The mean number of ETDRS letter gain showed a positive linear correlation with the mean number of anti-VEGF injections received (Pearson correlation coefficient, r = 0.78)[29,31,35–41,44–50,53] (Figures 1 and 2).

In the subgroup analysis stratified by prior treatment status, the correlation analysis showed a strong association between mean number of injections and mean letter gain in the naive patients (Pearson correlation coefficient, r = 0.73)[36,37,45–47,49] (Figure S13). However, a moderate association was observed in mixed treatment patients (Pearson correlation coefficient, r = 0.47)[29,31,38,39,41,44,48,50] (Figure S14).

Seven studies with the 3q4w followed by PRN regimen reported data for mean number of injections and BCVA. Limited evidence was available to establish a correlation between mean number of injections and BCVA gain at 12 months for conbercept[36,47] and aflibercept.[35] A positive linear correlation was observed between mean number of injections and BCVA gain for RAN 3q4w followed by PRN regimen (Pearson correlation coefficient, r = 0.59)[36,39,41,48,49] (Figure S15).

Correlation Between Baseline BCVA and Mean Change in BCVA at 12 Months

A correlation analysis in overall patients irrespective of prior treatment status showed that higher the baseline BCVA score lesser the BCVA gain at 12 months (Pearson correlation coefficient, r=−0.42).[29,31,35–41,43–54] In the subgroup analysis by prior treatment status, only the treatment-naive group corroborated this correlation with the Pearson correlation coefficient of r=−0.44.[36,37,43,45–47,49] A weak correlation (Pearson correlation coefficient, r=−0.24)-[29,31,38,39,41,44,48,50–52] was observed between baseline BCVA scores and mean change from baseline to 1 year in the BCVA letter score in mixed treatment patients (Figure 3).

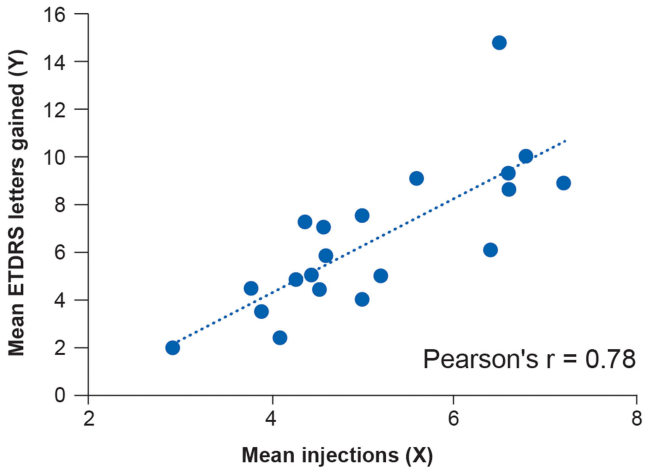
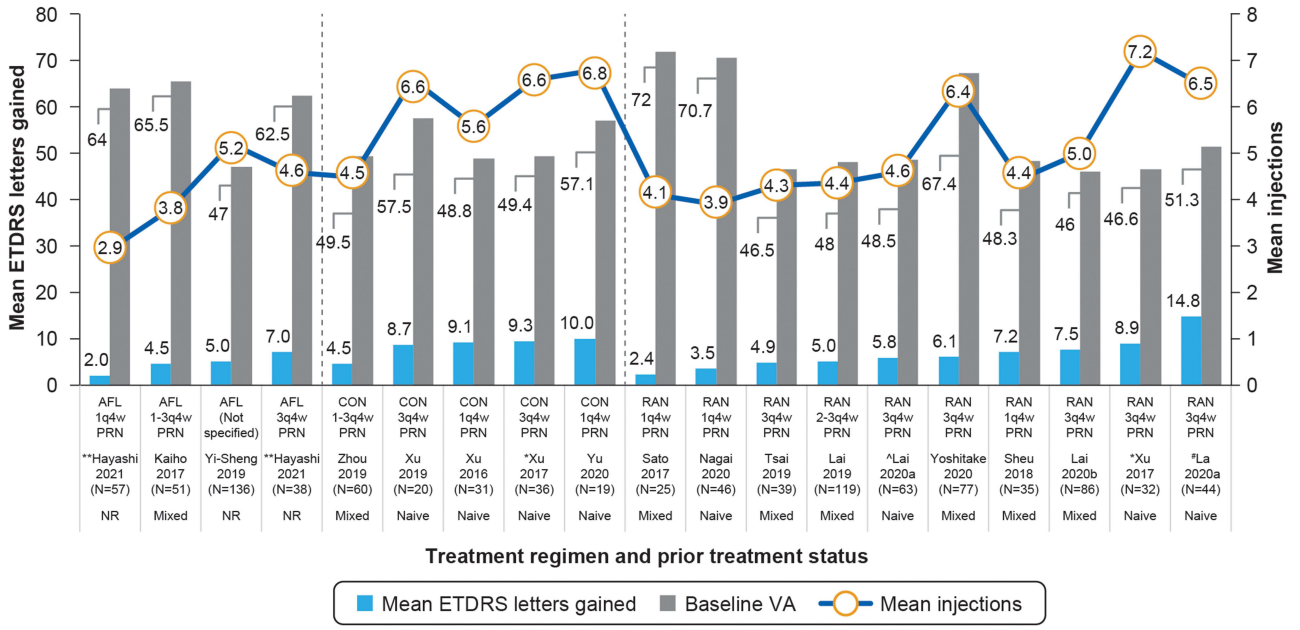


Figure 1 Correlation of BCVA gain with mean injections at 12 months for overall patients.
Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; BCVA, best corrected visual acuity.



Lai 2020a: ^before policy change (Up to 5 injections per year); #after policy change (Up to 8 injections per year);
*Data is from same study (Xu 2017); **Data is from same study (Hayashi 2021)

Figure 2 Mean injections and BCVA improvement at 12 months.
Abbreviations: AFL, aflibercept; CON, conbercept; ETDRS, Early Treatment Diabetic Retinopathy Study; RAN, ranibizumab; PRN, pro re nata; q4w, monthly dose; BCVA, best corrected visual acuity.

Retinal Thickness Outcomes

Most studies used similar definitions for retinal thickness, although a range of terminologies were used, including CRT, central subfield thickness, CMT, and central foveal thickness.

Mean Change in Retinal Thickness from Baseline at 12 Months

Twenty studies reported change in mean retinal thickness at 12 months. Baseline retinal thickness ranged from 381[52] to 538 µm,[35] and thickness at 12 months ranged from 276[37] to 414 µm.[35] The cumulative mean±SD reduction in retinal thickness with anti-VEGFs was 115.4±31.8 µm (cumulative mean±SD injections: 5.1±1.2). The cumulative mean±SD reduction in CRT values was 116.9±30.7 µm with ranibizumab (mean injections: 5), 105.9±20.8 µm with aflibercept (mean injections: 4.1), 81.7±70.2 µm with bevacizumab, and 135.2±18.2 µm with conbercept (mean injections: 6) (Table 4).

Ranibizumab. Ten studies reported the change in mean retinal thickness. The mean reduction in retinal thickness ranged from 62[29] to 149 µm.[51] RAN 3q4w followed by PRN regimen reported high reduction in mean retinal thickness (149 µm) in patients with a high baseline retinal thickness value (503 µm)[51] (Figure S16).

Aflibercept. Four studies reported the change in mean retinal thickness. The mean reduction in retinal thickness in patients treated with aflibercept ranged from 86.1[35] to 133.8 µm.[35] AFL 3q4w followed by PRN regimen with 4.6 mean injections reported the highest reduction in mean retinal thickness (133.8 µm)[35] (Figure S17).

Bevacizumab. Only 1 study reported thickness reduction data for bevacizumab (regimen details were unclear). The mean reduction in retinal thickness at the 12-month follow-up was 32 µm.[40]

Conbercept. Five studies reported the change in mean retinal thickness. The mean reduction in retinal thickness ranged from 103[44] to 146.1 µm.[44] Conbercept 3q4w followed by PRN regimen with 6.6 mean injections reported a high reduction (146.1 µm) in mean retinal thickness in patients with a high baseline retinal thickness (482 µm)[44] (Figure S18).

In the subgroup analysis stratified by prior treatment status, the cumulative mean±SD reduction in retinal thickness with all anti-VEGFs was 141.6±5.2 µm (cumulative mean±SD injections: 6.1±1.2) in naive patients and 108.8±27.5 µm (cumulative mean±SD injections: 4.6±0.8) in mixed treatment patients. Eight studies with the 3q4w followed by PRN regimen reported data for mean number of injections and retinal thickness outcomes at 12 months. Naive patients treated

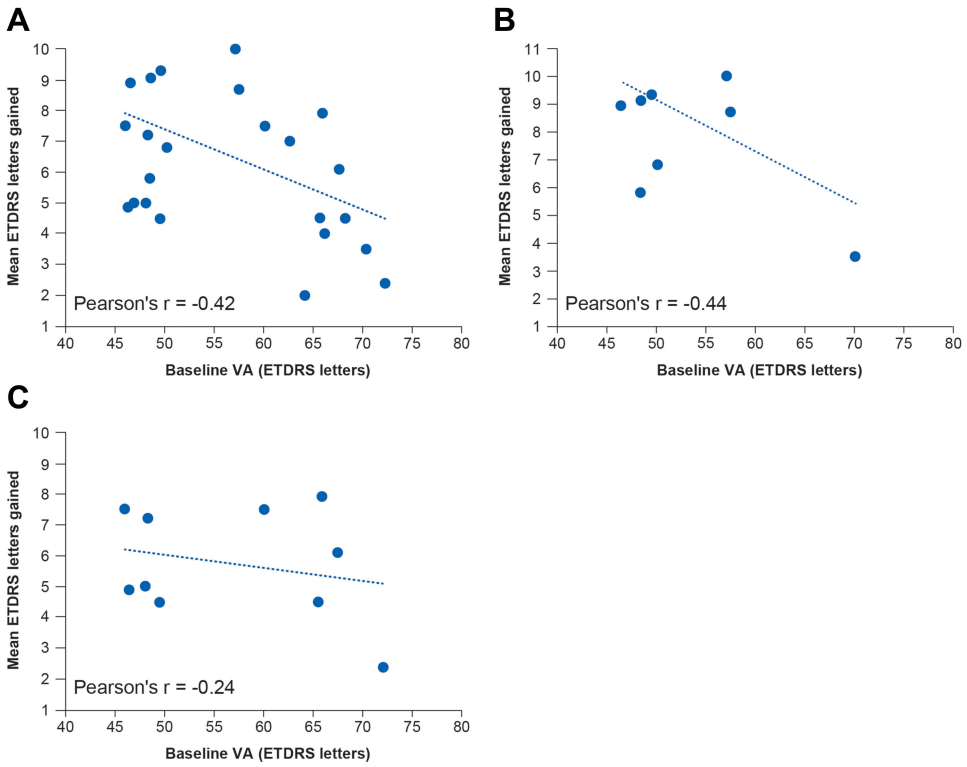


Figure 3 Correlation between baseline BCVA values and BCVA gain (ETDRS letters) at 12 months for **(A)** overall patients, **(B)** naive patients and **(C)** mixed treatment patients.
Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; BCVA, best corrected visual acuity.

with conbercept (mean injections: 6.6) and ranibizumab (mean injections: 7.2) showed a better reduction in retinal thickness of 146.1 and 145.2 µm, respectively, at the 12-month follow-up (Figure S19). Only 1 study each reported data for AFL 3q4w followed by PRN regimen (patients' prior treatment status unclear) and bevacizumab 3q4w followed by PRN regimen (naive patients), with a retinal thickness reduction of 133.8 µm (mean injections: 4.6)[35] and 131.3 µm (median injections: 6)[43] at 12 months, respectively.

Correlation Between Injection Frequency and Reduction in Retinal Thickness at 12 Months

Overall, 16 studies reported data on mean number of injections and reduction in retinal thickness from baseline at 12 months. A positive correlation was observed between mean reduction in CRT and mean number of injections, irrespective of anti-VEGF received (Pearson correlation coefficient, r = 0.54)[29,31,35–41,44–48,50,53] (Figure 4).

In the subgroup analysis stratified by prior treatment status, 5 studies reported correlation data between mean number of injections and retinal thickness outcome at the 12-month follow-up in patients naive to anti-VEGFs. A weak positive correlation was observed between mean number of injections and reduction in retinal thickness in patients naive to anti-VEGFs (Pearson correlation coefficient, r = 0.18)[36,37,45–47] (Figure S20).

Eight studies reported correlation data between mean number of injections and retinal thickness outcome at the 12-month follow-up in patients with mixed treatment status to anti-VEGFs. A positive correlation was observed between mean number of injections and reduction in retinal thickness in patients with mixed treatment status to anti-VEGFs (Pearson correlation coefficient, r = 0.60)[29,31,38,39,41,44,48,50] (Figure S21).

Correlation Between Baseline CRT with Baseline BCVA

While higher baseline CRT was associated with poor baseline BCVA in naive patients (Pearson correlation coefficient, r= −0.83),[36,37,43,45–47] it was associated with better baseline BCVA in mixed treatment patients (r = 0.67)[29,31,38,39,41,44,48,50–52] (Figure 5).

Table 4 Change in Retinal Thickness Outcomes at 12 Months

Study Details (Author and Year, Sample Size (N), Prior Treatment Status	Treatment	Baseline CRT (μm)	CRT at 12 Months (μm)	Change from Baseline to 12 Months, Reduction in CRT (μm)	Mean No. of Injections
Seo 2016[52] (N=55), Mixed	Ranibizumab	381.7	287	−94.7	–
Sheu 2018[29] (N=35), Mixed	Ranibizumab	399.8	337.9	−61.9	4.43
Tsai 2019[41] (N=39), Mixed	Ranibizumab	406	329	−77	4.3
Nagai 2020[37] (N=46), Naive	Ranibizumab	418	276	−142	3.9
Lai 2020b[48] (N=86), Mixed	Ranibizumab	430	302	−128	5
Lai 2019[50] (N=119), Mixed	Ranibizumab	446.5	338.1	−108.4	4.36
Xu 2017[36] (N=32), Naive	Ranibizumab	473.9	328.7	−145.2	7.2
Yoshitake 2020[39] (N=77), Mixed	Ranibizumab	475	331	−144	6.4
Sato 2017[31] (N=25), Mixed	Ranibizumab	492	374	−119	4.1
Murakami 2018[51] (N=40), Mixed	Ranibizumab	503	354	−149	–
Cumulative mean for ranibizumab: 10 studies, Mean ±SD		**442.6 ±41.9**	**325.8±29.8**	**−116.9±30.7**	**5±1.2**
Yi-Sheng 2019[53] (N=136), NR	Aflibercept	412.5	292.8	−119.7	5.2
Kaiho 2017[38] (N=51), Mixed	Aflibercept	489.6	386.6	−103	3.8
Hayashi 2021[35] (N=57), NR	Aflibercept 1q4w	501	414.4	−86.1	2.93
Hayashi 2021[35] (N=38), NR	Aflibercept 3q4w	538	403.9	−133.8	4.58
Kimberly 2018[56] (N=29), Pre-treated	Aflibercept	–	–	−87	–
Cumulative mean for Aflibercept: 4 studies (5 treatment arms), Mean±SD		**485.3 ±52.7**	**374.4±55.6**	**−105.9±20.8**	**4.1±1.0**
Sepehr 2019[40] (N=231), NR	Bevacizumab	428	396	−32	5
Choovuthayakorn 2020[43] (N=423), Naive	Bevacizumab	496.8	365.5	−131.3	–
Cumulative mean for bevacizumab: 2 studies, Mean ±SD		**462.4 ±48.6**	**380.8±21.6**	**−81.7±70.2**	
Zhou 2019[44] (N=60), Mixed	Conbercept	454	351	−103	4.5
Yu 2020[45] (N=19), Naive	Conbercept	460	316.5	−143.4	6.8
Xu 2017[36] (N=36), Naive	Conbercept	469	330.9	−138.4	6.6
Xu 2019[47] (N=20), Naive	Conbercept	482	336	−146.1	6.6
Xu 2016[46] (N=31), Naive	Conbercept	487	342.1	−145.1	5.6
Cumulative mean for conbercept: 5 studies, Mean ±SD		**470.4±14**	**335.3±12.9**	**−135.2±18.2**	**6±1**
Cumulative mean for overall anti-VEGFs: 20 studies, Mean±SD		**459.2 ±40.9**	**342.5±37.2**	**−115.4±31.8**	**5.1±1.2**

Abbreviations: CRT, central retinal thickness; NR, not reported; SD, standard deviation; VEGF, vascular endothelial growth factor.

Correlation Between Baseline CRT and BCVA Outcomes at 12 Months

Overall, a weak positive correlation was observed between baseline retinal thickness and BCVA letter score at the 12-month follow-up (Pearson correlation coefficient, r=0.35)[29,31,35–41,43–48,50–53] (Figure 6).

In the subgroup analysis stratified by prior treatment status, a strong negative correlation was observed between baseline retinal thickness and BCVA letter score at the 12-month follow-up in patients naive to anti-VEGFs (Pearson correlation coefficient, r=−0.81).[36,37,43,45–47] However, contradictory positive results were observed between baseline thickness and BCVA letter score at 12 months in the mixed treatment patients (Pearson correlation coefficient, r = 0.62)[29,31,38,39,41,44,48,50–52] (Figure 6).

In the overall group, no correlation was observed between baseline retinal thickness and mean change from baseline to 1 year in the BCVA letter score. However, in the subgroup analysis stratified by prior treatment status, strong positive (Pearson correlation coefficient, r=0.61)[36,37,43,45–47]and weak negative (Pearson correlation coefficient, r=−0.38)[29,31,38,39,41,44,48,50–52] correlations were observed between baseline retinal thickness and BCVA letter gain at the 12-month follow-up in naive patients and mixed treatment patients, respectively (Figure 7).

Correlation Between Change in CRT and Change in BCVA at 12 Months

A weak positive correlation was observed between change in CRT and change in BCVA. At 12 months, a higher reduction in CRT was associated with a higher BCVA gain. However, this association was weak in all the groups, patients naive to anti-VEGFs (r = 0.29),[36,37,43,45–47] mixed treatment patients (r = 0.11),[29,31,38,39,41,44,48,50–52] and overall patients (r = 0.50)[29,31,35–41,43–48,50–53] (Figure 8).

Correlation Between CRT and BCVA at 12 Months

Higher CRT was associated with poor BCVA in patients naive to anti-VEGFs (r=−0.81)[36,37,43,45–47] at 12 months (Figure 9). However, in the mixed treatment patients (r = 0.35)[29,31,38,39,41,44,48,50–52] and in the overall patients (r = 0.26),[29,31,35–41,43–48,50–53] a higher CRT was associated with better BCVA at 12 months.

Regression Analysis

The multivariate linear model for predicting the BCVA gain included baseline BCVA data, baseline CRT data, and mean number of injections. The coefficient of determination R squared (R^2) and adjusted R^2 values for this model were 0.786 and 0.74. In this model, baseline BCVA and mean number of injections were significantly associated with final BCVA ETDRS letter gain (p = 0.02 and 0.0001, respectively). However, the relationship between baseline CRT and BCVA gain was not significant (p = 0.184) (Table 5).

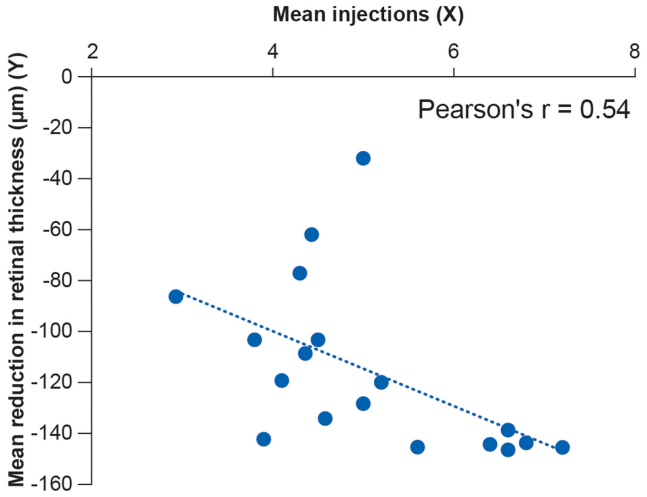
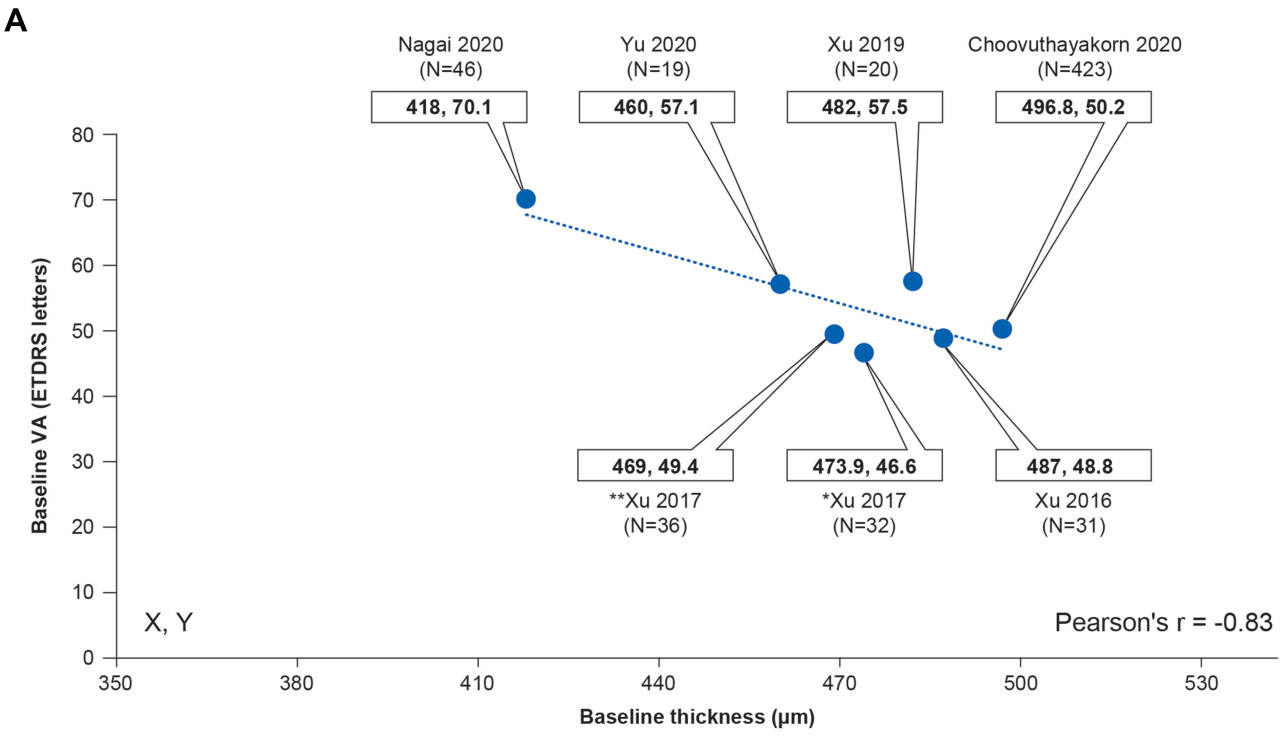


Figure 4 Correlation between reduction in retinal thickness and mean injections at 12 months for overall patients.



*Data is from same study; *Xu 2017 (N=32) is for ranibizumab treatment and **Xu 2017 (N=36) is for conbercept treatment

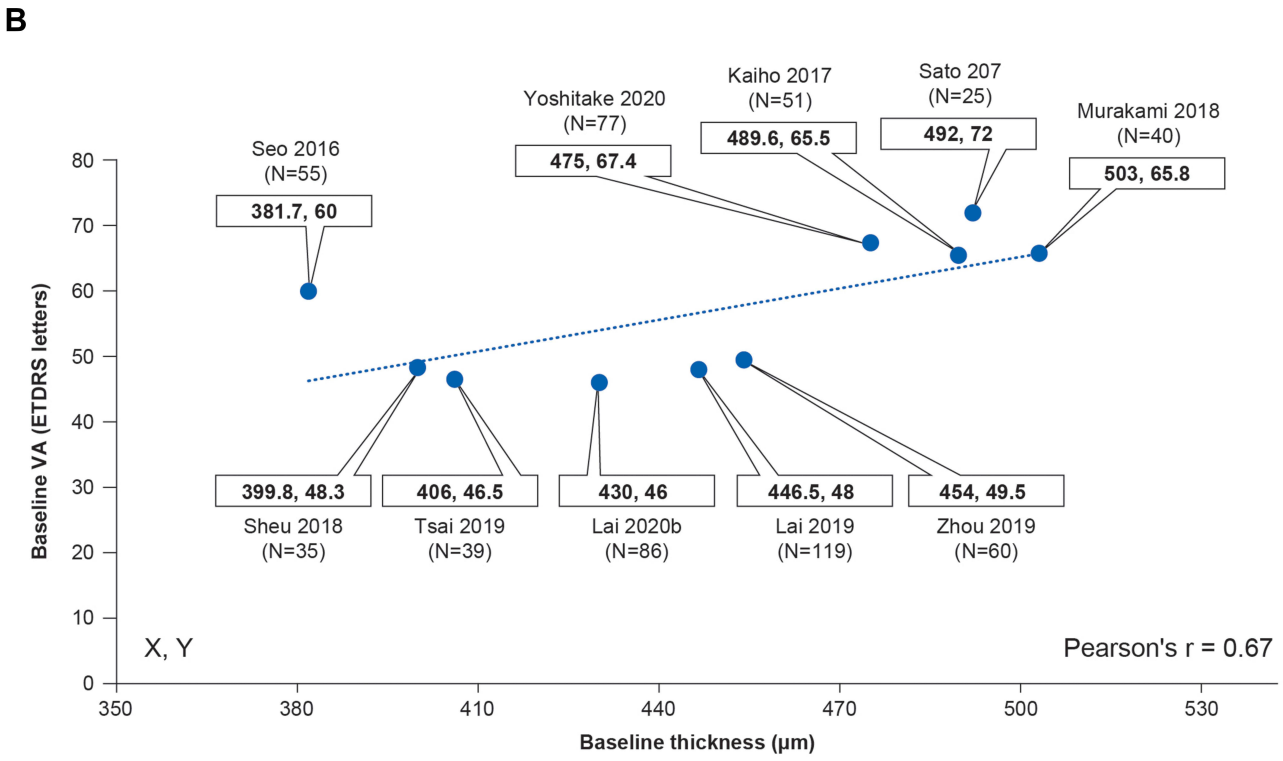


Figure 5 Correlation between baseline CRT and baseline BCVA for **(A)** naive patients and **(B)** mixed treatment patients.

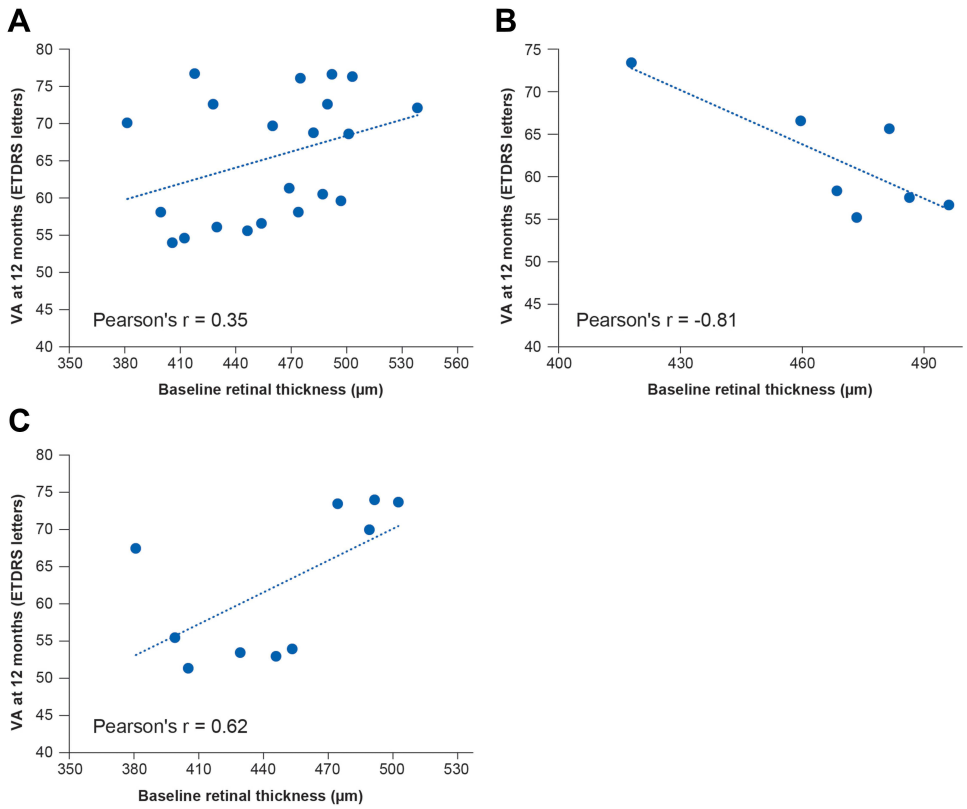


Figure 6 Correlation between baseline CRT and BCVA letter score at 12 months for **(A)** overall patients, **(B)** naive patients and **(C)** mixed treatment patients.
Abbreviations: CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity.

Retinal Fluid Outcomes

Eight studies reported retinal fluid outcomes at baseline, whereas only 1 study reported fluid outcome data at the 12-month follow-up. Patients treated with bevacizumab reported a significant reduction in total intraretinal fluid (mean±SD at baseline: 0.25±0.24 mm^3; at 12 months: 0.10±0.14 mm^3; p = 0.001) and subretinal fluid (mean±SD at baseline: 0.04 ±0.18 mm^3; at 12 months: 0.002±0.01 mm^3; p = 0.048) within 3-mm area at 12 months.[54]

Clinical Visits

Only 1 study reported the number of ophthalmologic clinic visits. In this study, patients were receiving bevacizumab injection. The median number of clinic visits was higher in the first year (10; interquartile range [IQR]: 8–12) compared with that in the second (7; IQR: 4–9) and third year (6; IQR: 3–9).[43]

Tolerability and Switching

Treatment discontinuations were not commonly reported in real-world studies. Only 2 studies reported discontinuation data. Of 234 patients from the Kelkar study, 127/234 patients were lost to follow-up at 12 months. Of these 127 patients, 64 were from the ranibizumab group and 63 were from the bevacizumab group.[57] In another study, of the 55 patients treated with ranibizumab, 6 (4 lost to follow-up and 2 withdrew consent) discontinued from the study before 12 months.[52]

Safety

Of the 21 studies reporting safety data, only 6 reported adverse events (AEs) (Table 6). None of the studies reported any serious ocular AEs. One study reported data for conjunctival hemorrhages, which were higher in the conbercept-treated group (15.6%, 5/32 patients) compared with the ranibizumab-treated group (10%, 3/30 patients) during 12 month follow-

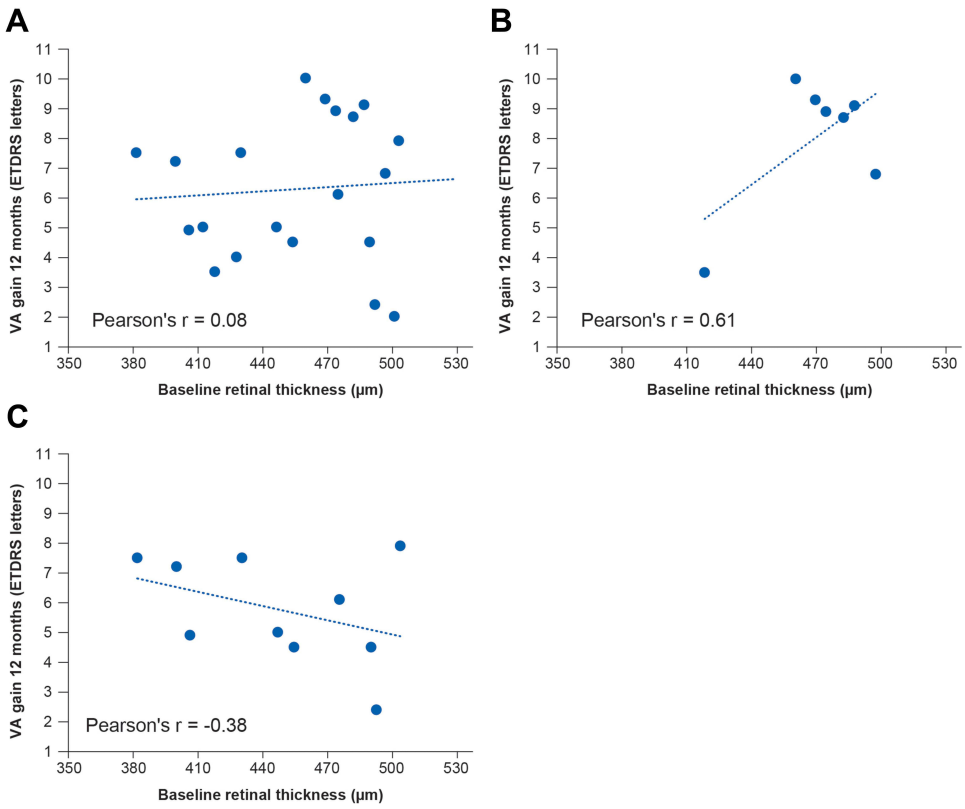


Figure 7 Correlation between baseline CRT and BCVA gain at 12 months for **(A)** overall patients, **(B)** naive patients and **(C)** mixed treatment patients.
Abbreviations: CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity.

up.[36] Two studies reported a rise in intraocular pressure (IOP) with bevacizumab injections,[58,59] while 1 study reported a rise in IOP with the ranibizumab[36] and conbercept[36] regimens. One study reported injection-related endophthalmitis with bevacizumab (0.11%) and ranibizumab (0.42%).[24] None of the included studies reported major systemic AEs with intravitreal anti-VEGF injections.

Discussion

In the current SLR, clinical evidence from real-world studies on visual outcomes and anatomical outcomes with intravitreal anti-VEGF injections were analyzed in the management of DME.

Overall, the studies were comparable in terms of baseline characteristics such as age, gender, and baseline glycated hemoglobin levels. However, the studies varied in prior treatment status/type of prior therapies, time point of assessment, number of injections, treatment regimen, and baseline BCVA. None of the studies in this SLR included patients with good BCVA (20/25 or better on the Snellen chart) at baseline, which contrasts with DRCR protocol V[60] (DRCR protocol V includes patients with good BCVA, ie, 20/25 or better on the Snellen chart). This suggests that, in routine clinical practice, most physicians are not treating patients with good BCVA at baseline.

Use of prior anti-VEGFs at baseline is an important parameter that was not consistently reported across the included studies. In this review, most studies included a mixed treatment patients (both naive patients and previously treated patients). However, in randomized controlled trials, patients were mostly either treatment naive or had undergone a wash-out period before commencing DME treatment.[61]

A large variability was observed across studies in the mean number of anti-VEGF injections received at 12 months. In this review, the mean number of anti-VEGF injections ranged from 2.9[35] to 7.2,[36] with a cumulative mean of 5.2. In contrast, the DRCR protocol T study reported the median number of injections as 9 or 10.[62] In the current review, the mean number of injections in the first 12 months was less compared with that in DRCR protocol T, where 5–6 loading

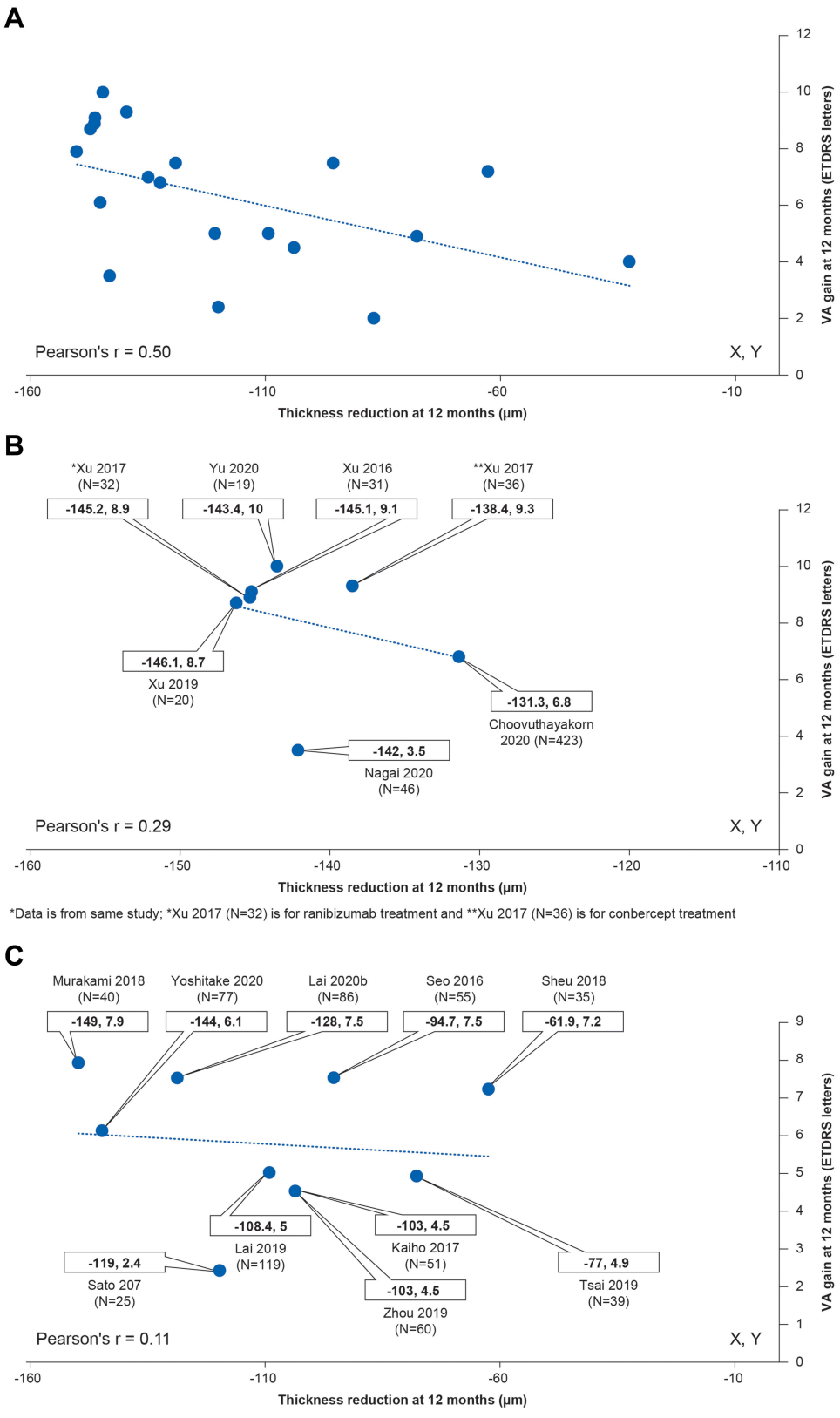


Figure 8 Correlation between reduction in retinal thickness and BCVA gain at 12 months for **(A)** overall patients, **(B)** naive patients and **(C)** mixed treatment patients.
Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity.

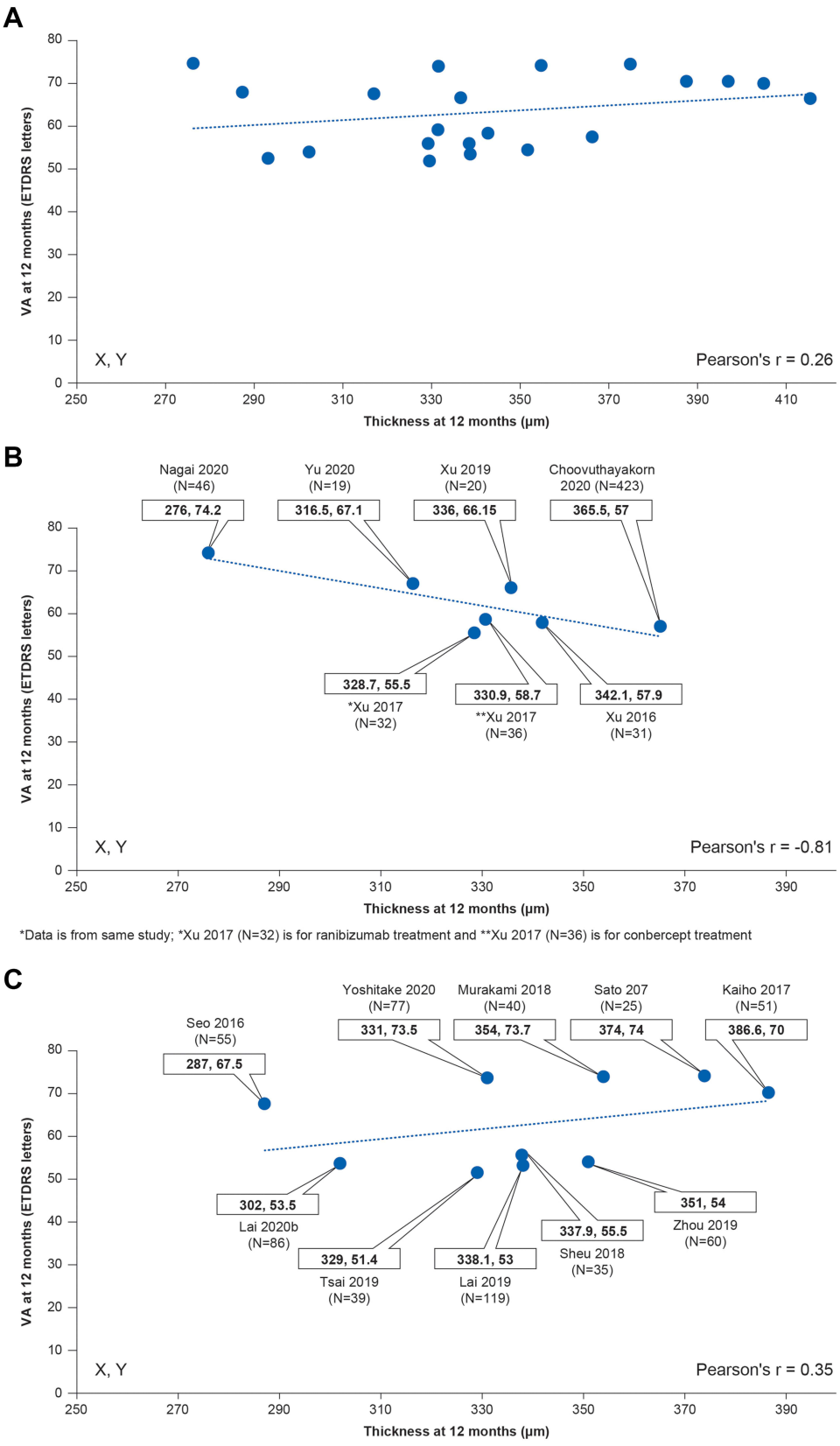


Figure 9 Correlation between CRT and BCVA letter score at 12 months for **(A)** overall patients, **(B)** naive patients and **(C)** mixed treatment patients.
Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity.

Table 5 Baseline Factors (BCVA and CRT) and Mean Number of Injections for Mean Change of ETDRS Letters by Multiple Regression Models

Variable	ß Coefficient	*P*-value	R Square	Adjusted R Square	*F*
Baseline BCVA	−0.099	0.0208	0.786	0.74	17.19
Baseline CRT	0.013	0.1842			
Mean number of injections at 12 months	1.424	0.0001			

Abbreviations: CRT, central retinal thickness; BCVA, best-corrected visual acuity.

Table 6 Summary of Adverse Events with Anti-VEGF Agents

Author and Year	Intervention	Follow-Up Period	Sample Size	Ocular AEs, n (%)	Non-Ocular AEs, n (%)
Roh 2010[58]	BEV	Immediately after injection	56 eyes (43 patients)	Rise in IOP: 3 (5.4%)	–
Masahiko 2019[74]	AFL	6 months	508 patients	Retinal detachment: 0.39%	Cerebral infarction: 0.79%
Seo 2016[52]	RAN	12 months	55 eyes (55 patients)	Vitreous hemorrhage: 4 (7.3%)	–
Xu 2017[36]	CON	12 months	36 eyes (32 patients)	Conjunctival hemorrhage: 5 (15.6%), eye pain: 5 (15.6%), rise in IOP: 4 (12.5%), vitreous hemorrhage: 1 (3.1%), vitreous floaters: 1 (3.1%), macular fibrosis: 1 (3.1%), corneal abrasion: 1 (3.1%), dry eye: 1 (3.1%)	Hypertension: 2 (6.25%)
	RAN	12 months	32 eyes (30 patients)	Conjunctival hemorrhage: 3 (10%), eye pain: 4 (13.3%), rise in IOP: 3 (10%), vitreous floaters: 1 (3.3%), corneal abrasion: 1 (3.3%)	Hypertension: 3 (10%)
Kanchanaranya 2015[24]	BEV	5 years	933 injections	Endophthalmitis, 1 (0.11%)	–
	RAN	5 years	236 injections	Endophthalmitis: 1 (0.42%)	–
Jain 2017[59]	BEV	3 years	–	Rise in IOP: 1	–

Abbreviations: AE, adverse event; AFL, aflibercept; BEV, bevacizumab; CON, Conbercept; RAN, Ranibizumab; IOP, intraocular pressure.

doses were given followed by continued regular treatment until stability. In this review of Asian studies, the cumulative mean number of injections of ranibizumab during first 12 months was 5.2, this is similar to other real-world studies conducted in non-Asian countries.[63–65] The cumulative mean number of injections of aflibercept during first 12 months in Asian studies was 4.6, which is less compared to the mean number of injections reported from other real-world studies.[66–69]

In this review, <50% of the real-world studies reported an initial loading dose of 3 monthly doses, which was followed by a variation of an as-needed (PRN) or other regimens. This is in contrast to randomized controlled trials.

In this SLR, the mean improvement in the BCVA score, with at least a 7-letter gain, was greater with conbercept (80%, 4/5 studies), followed by ranibizumab (50%, 6/12 studies) and aflibercept (25%, 1/4 studies), at 1 year. At least 40% of patients who received ranibizumab,[29,36,49] conbercept[36,46] and bevacizumab[43] injections reported a gain of ≥10 ETDRS letters compared with 25% of patients who received aflibercept.[53] The improvement in BCVA varied with the baseline BCVA and mean number of injections received. In addition, treatment-naive patients were more

likely to report greater improvements in BCVA over 12 months compared with patients previously treated with anti-VEGFs.

The mean improvement from baseline in BCVA gain was 6.9 ETDRS letters after 1 year of treatment in patients with DME. In this SLR, conbercept (8.3±2.2) and ranibizumab (6.8±3.2) treatment reported better cumulative mean±SD BCVA gain than aflibercept (4.6±2.1) and bevacizumab (4.9±1.6) at the 12-month follow-up. In contrast, the DRCR protocol T study reported better vision gain in change from baseline in the letter score (mean±SD) with aflibercept (13.3 ±11.1), followed by ranibizumab (11.2±9.4) and bevacizumab (9.7±10.1), at the 12-month follow-up.[62] However, given the variation in baseline BCVA, frequency of injections, treatment-naive status, and other limitations in the analysis of real-world data, no definitive conclusions can be made regarding the relative efficacy of anti-VEGF agents. The other limitation of this review is, we did not use weighted means, weighing the outcome according to number of observations provides robust results. It was not possible to calculate weighted means with the evidence reported in these real-world studies. In addition, the outcomes in naive patients are not comparable to pre-treated patients and/patients with mixed treatment status. Hence, we have provided data for each subgroup to reflect the results for these patient subgroups. However, in some studies, the detail of previous treatment is unclear/not reported and hence we have also reported data for overall studies irrespective of their prior treatment status.

In the subgroup analysis stratified by prior treatment status, ranibizumab showed similar BCVA letter gain (mean ±SD) in naive patients (8.3±4.9) in the real-world setting[36,37,49] compared with that in the DRCR protocol T study (7 ±8.1) at the 12-month follow-up.[62]

In this review, at the 12-month follow-up, all studies demonstrated a mean reduction in CRT. Reduction in CRT was also observed with anti-VEGF treatment in the DRCR protocol T study.[62] In this SLR, at the 12-month follow-up, the mean±SD reductions in CRT on optical coherence tomography were 135.2±18.2 μm with conbercept, 116.9±30.7 μm with ranibizumab, 105.9±20.8 with aflibercept, and 81.7±70.2 with bevacizumab.

Notably, in Taiwan, a health care policy change allowing reimbursement of more ranibizumab injections (before policy change: up to 5 vs after policy change: up to 8) was associated with improved BCVA and retinal thickness outcomes,[49] thereby supporting the observation that a higher improvement in the mean BCVA score was associated with increased injection frequency over 12 months.

At 12 months, the correlation between the BCVA letter scores and retinal thickness in DME patients treated with anti-VEGF agents reported contrasting results compared with previous findings.[70] Higher retinal thickness at 12 months was associated with better BCVA in overall (r = 0.26) and mixed treatment patients (r = 0.35) with DME. This weak correlation implies that improved BCVA is likely multifactorial and does not depend on the thickness of the retinal layers alone; moreover, from a clinical perspective, the correlation between retinal thickness and BCVA may be confounded by patients with ischemic maculopathy, whereby the thin atrophic macula is accompanied by poor vision.

The burden of health care visits in DME patients is high,[71] although the DRCR.net studies have demonstrated a reduction in the frequency of injections after the first year with intensive treatment.[62,72] PRN approach refers to monthly visit/control. However, some studies followed-up the patients monthly, and some studies employed a specific reinjection/revisit criteria based on predefined disease stability criteria as defined by the physician and some studies did not report this information. The studies included in this review did not clearly specify the evidence on clinic visits. Only 1 study reported median clinic visits for bevacizumab for the first, second, and third year, with a decrease in the number of clinic visits of 10, 7, and 6, respectively.[43]

All 4 anti-VEGFs (aflibercept, bevacizumab, conbercept, and ranibizumab) had comparable ocular and non-ocular safety profiles. In this review, the incidence of rise in IOP ranged from 1% to 5.6% with anti-VEGFs. In a similar type of real-world evidence literature review, the incidence of rise in IOP ranged between 10% and 20%.[73]

Conclusions

This SLR of real-world observational studies from Asia found that ranibizumab was the most frequently used anti-VEGF for DME compared with other anti-VEGFs. Off-label bevacizumab was also frequently used for DME treatment in several Asian countries; however, conbercept was used only in China. This might be due to the longest availability of ranibizumab, and bevacizumab compared to other anti-VEGFs in Asia. Treatment regimens varied across the studies. The

loading dose regimen was the most frequently followed approach for ranibizumab, whereas for the other anti-VEGFs, no loading dose regimen was described. A loading dose followed by an as-needed (PRN) approach was more commonly used than a T&E approach. The mean number of anti-VEGF injections was lower compared with that in the randomized controlled trials at the 12-month follow-up, which may account for the lower improvement in mean BCVA. A greater letter gain was observed in naive patients compared with that in mixed treatment patients (naive and previously treated group). The correlation analysis suggested that a higher mean number of injections was associated with better BCVA gain for all the 3 anti-VEGFs (ranibizumab, aflibercept, and conbercept). This correlation was stronger in naive patients than in mixed treatment patients. Similarly, a higher mean number of injections was associated with a greater reduction in CRT for all the 3 anti-VEGFs (ranibizumab, aflibercept, and conbercept). In the multivariate regression analysis, baseline BCVA and mean number of injections were significantly associated with final BCVA ETDRS letter gain at 12 months.

Overall, a weak positive correlation was observed between baseline retinal thickness and BCVA letter score at the 12-month follow-up. There was a paucity of data for retinal fluid, clinical visits, and treatment switching outcomes across the included studies. Overall, no conclusion regarding the comparative efficacy of the anti-VEGFs could be drawn owing to heterogeneous study population, treatment posology, and frequency of injections, with few studies reporting head-to-head data.

Abbreviations

1q4w, 1 dose at baseline; 3q4w, 3 monthly loading doses; AE, adverse event; AFL, aflibercept; BCVA, best-corrected visual acuity; BEV, bevacizumab; CFB, change from baseline; CI, confidence interval; CMT, central macular thickness; CON, conbercept; CRT, central retinal thickness; DME, diabetic macular edema; DRCR, Diabetic Retinopathy Clinical Research; ETDRS, Early Treatment Diabetic Retinopathy Study; IOP, intraocular pressure; IQR, interquartile range; IVR, intravitreal ranibizumab; IVTA, intravitreal triamcinolone acetonide; LogMAR, logarithm of the minimum angle of resolution; MGP, modified grid laser photocoagulation; NR, not reported; PRN, pro re nata; q4w, monthly dose; RAN, ranibizumab; RAZ, razumab; RWE, real-world evidence; SD, standard deviation; SLR, systematic literature review; T&E, treat and extend; VEGF, vascular endothelial growth factor.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

IHT (Novartis Singapore Pte Ltd.), PB, and JS (Novartis Healthcare Pvt. Ltd.) are Novartis employees. RKM was an employee of Novartis when the review was being conducted. YSY, GSWT, and NYG have acted as consultants for Novartis for this work and other work. YSY is a consultant for Roche and receives financial support from Bayer. GSWT is a consultant for Roche, Bayer, Allergan, Zeiss, Nikon-Optos, Topcon, and Leica, has received grants from Santen, and owns equity in Eyris. NYG receives financial support from Bayer. The authors report no other conflicts of interest related to this work.

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