Aflibercept for diabetic macular oedema: a Meta-analysis of randomized controlled trials

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Abstract
● **AIM:** To evaluate the relative efficacy and safety of aflibercept for treatment of diabetic macular oedema (DMO).
● **METHODS:** A comprehensive search in MEDLINE, CENTRAL and EMBASE was undertaken for randomized controlled trials (RCTs) comparing intravitreal anti-vascular endothelial growth factor (anti-VEGF) versus another treatment. Primary outcome measures were proportion of patients with at least 15 letters of gain or loss on a logMAR visual acuity chart, and change in best corrected visual acuity (BCVA) and central macular thickness (CMT) from baseline. Safety outcomes were rates of death, thromboembolic events and any systemic or ocular serious adverse events. The final search was performed on November 2017.
● **RESULTS:** Four RCTs were included. Only one trial compared efficacy and safety of aflibercept with bevacizumab and ranibizumab over 1 or 2y. Three trials were included for Meta-analysis comprising 661 patients (331 in the aflibercept, and 330 in the photocoagulation group). Aflibercept was more efficacious compared to photocoagulation in the proportion of patients with at least 15 letters of improvement and worsening, and in improvement of BCVA and reduction in CMT at 1 or 2y. The safety estimates at 1 or 2y did not differ statistically.
● **CONCLUSION:** Aflibercept offers superior benefits over photocoagulation in improving and preserving vision, with no differences in safety. Further comparative effectiveness trials between aflibercept and other anti-VEGF agents will aid ophthalmologists in treatment decisions.
● **KEYWORDS:** aflibercept; diabetic macular oedema; Meta-analysis; randomized controlled trial

INTRODUCTION

Diabetic macular oedema (DMO) is a common complication of diabetic retinopathy (DR), and a major cause of vision loss[1]. The increasing prevalence of diabetes worldwide highlights the importance of DMO treatment[2]. Grid or focal laser photocoagulation of the macula has been demonstrated to lower the risk of vision loss in DMO, but vision is rarely improved[3]. Vascular endothelial growth factor (VEGF) is a key mediator of abnormal vascular permeability in DMO[4]. Intravitreal anti-VEGF injections have been demonstrated to produce better outcomes compared to photocoagulation which had been the standard treatment for DMO prior[5-13].

The most used intravitreal anti-VEGF agents, aflibercept (Eylea, Regeneron-Bayer HealthCare), bevacizumab (Avastin, Genentech) and ranibizumab (Lucentis, Genentech), which have been demonstrated to be effective and relatively safe in treatment of DMO[5,14-17]. Aflibercept, a human recombinant fusion protein that binds VEGF-A and placental growth factor (PGF) to inhibit activation of VEGF receptors, has been investigated in trials on patients with DMO[11,15,18-20]. Aflibercept binds to VEGF-B and PGF, which are mediators involved in abnormal vascular permeability and retinal neovascularization, while ranibizumab and bevacizumab do not[21-22].

Intravitreal aflibercept has been approved for treatment of DMO in the United States, Europe, Japan, and Australia. The efficacy and safety of intravitreal aflibercept for DMO compared with photocoagulation has been demonstrated in the DA VINCI trial[11,20]. The subsequent studies, VISTA and VIVID, demonstrated that after nearly 3y of treatment, intravitreal aflibercept demonstrated superior visual and anatomic outcomes compared with photocoagulation. Ocular and systemic safety outcomes after nearly 3y of treatment were similar between aflibercept and photocoagulation[15]. The Diabetic Retinopathy Clinical Research Network (DRCRN) recently conducted a randomized clinical trial (RCT) assessing comparative efficacy and safety for intravitreal aflibercept, bevacizumab and ranibizumab for treatment of DMO[18-19].

As DMO may cause significant visual impairment, there is need for continuing evidence-based recommendations to be established regarding efficacy and safety of anti-VEGF agents as newer data become available. This Meta-analysis evaluates the relative efficacy and safety of aflibercept for treatment of DMO.

SUBJECTS AND METHODS

This meta-analysis was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy to Identify Eligible Studies A systematic literature review with searches of CENTRAL (The Cochrane Library 2017, Issue 4), Ovid MEDLINE, EMBASE, the Meta Register of Controlled Trials (mRCT), ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP). The final search was conducted on November 2017.

Inclusion and Exclusion Criteria Articles were considered for inclusion in the Meta-analysis if the study design was an RCT, the population was patients with DR and clinically significant macular oedema (CSMO)[3], and the intervention was aflibercept compared to another treatment. All trials had at least one year of follow up. Studies evaluating different doses of aflibercept compared with each other, with no control or comparator, and studies where aflibercept was used in combination with other treatments were excluded. Conference abstracts and full reports without raw data available, letters, reviews, duplicate publications and studies not available in English were excluded.

Types of Effect Estimates Efficacy was assessed as the proportion of patients with at least 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (equivalent to 3 ETDRS lines or 0.3 logMAR) of gain or loss after one year or two years. Other measures of efficacy included mean change in best corrected visual acuity (BCVA), and mean reduction in central macular thickness (CMT) after one year or two years. Safety was assessed as the proportions of patients with death, thromboembolic events, and any systemic or ocular serious adverse event after one year or two years.

Selection of Studies Two review authors independently assessed the titles and abstracts found through the electronic searches (Nguyen CL, Wong E). Each record was classified as 'not relevant', 'possibly relevant', or 'definitely relevant'. Full-text reports were obtained for all records classified as 'possibly relevant' or 'definitely relevant' and then assessed to be included in the study (Nguyen CL, Wong E). Disagreement was settled with a third reviewer. Authors of studies were contacted for further details as needed to make adequate assessments.

Data Extraction Two reviewer authors independently extracted the data (Nguyen CL, Wong E). Discrepancies were settled with a third reviewer. The information extracted from each study included details on study methods, patients, interventions, the proportion of patients with at least 15 ETDRS letters of worsening and improvement, the mean change in BCVA and mean reduction in CMT measured after one year or two years, and the frequency of systemic and ocular adverse events.

Qualitative Assessment Two review authors independently assessed the study quality. With the RCTs the authors used the risk of bias tool recommended by the Cochrane Collaboration as per methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Nguyen CL, Wong E)[23]. Potential sources of bias in the following different domains were critically assessed: sequence generation, allocation concealment, blinding of patients, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. For each domain, the authors judged whether the risk of bias of that domain was high, low, or unclear. Authors of RCTs were contacted for information to adequately assess a study.

Statistical Analysis Quantitative data were recorded using Review Manager (RevMan, version 5.3). For continuous variables, the weighted mean difference was measured. For dichotomous variables, the risk ratios (RR) were measured. These were reported with a 95% confidence interval (CI), and $P<0.05$ was statistically significant on the test for overall effect. The I^2-statistic was used to assess heterogeneity between studies ($P<0.05$ was statistically significant heterogeneity)[24]. A random-effects model was utilized if there was heterogeneity between studies. Otherwise, a fixed effects model was used.

RESULTS

Overall Characteristics of Included Trials and Quality Assessment A total of 1745 articles were initially identified and of these 1695 were rejected. The 50 remaining articles with full texts were assessed for eligibility[11,15,18-20,25-26]. A total of 4 studies were included. One study compared aflibercept with bevacizumab and ranibizumab for centre-involved DMO[18-19]. As this was the only study comparing aflibercept with other anti-VEGF agents and there was no photocoagulation control arm, it was excluded from the Meta-analysis. Three trials compared aflibercept with control with up to 148wk of follow up. Meta-analysis was conducted on the trials at follow up of 1 and 2y[26]. In total, there were four RCTs included in this study. Three of these trials were included in the Meta-analysis, and comprised a total of 661 patients: 331 patients in the aflibercept group and 330 patients in the photocoagulation group (Figure 1). The characteristics of the studies included and risk of bias assessment are summarized in Table 1 and Figure 2.

The DA VINCI study compared photocoagulation with monthly, bimonthly and as needed or *pro re nata* (PRN) intravitreal aflibercept regimens. The PRN regimen was chosen for data extraction as this is the present practice with other anti-VEGF agents. The VISTA and VIVID studies compared photocoagulation with 4-weekly intravitreal aflibercept (2q4), and a regimen of five initial 4-weekly intravitreal aflibercept followed by 8-weekly injections (2q8). The 2q8 regimen was selected for data extraction as the complete number of injections in the first year was smaller, and this is comparable to PRN regimens of other studies. The DRCRN trial randomly

Table 1 Characteristics of randomized controlled trials of aflibercept included in this review

Study	Location	Comparator intervention	Follow up (wk)	n	Mean age (y)
DA VINCI 2012	United States, Canada, Austria	Laser photocoagulation	52	45/44[a]	61/64[a]
DRCRN 2016	United States	Bevacizumab 1.25 mg, Ranibizumab 0.3 mg	104	208/206/206[b]	61/62/59[b]
VISTA 2015	United States	Laser photocoagulation	148	151/154[a]	63/62[a]
VIVID 2015	Europe, Japan, Australia	Laser photocoagulation	148	135/132[a]	64/64[a]

[a]Aflibercept group/laser photocoagulation group; [b]Aflibercept group/bevacizumab group/ranibizumab group.
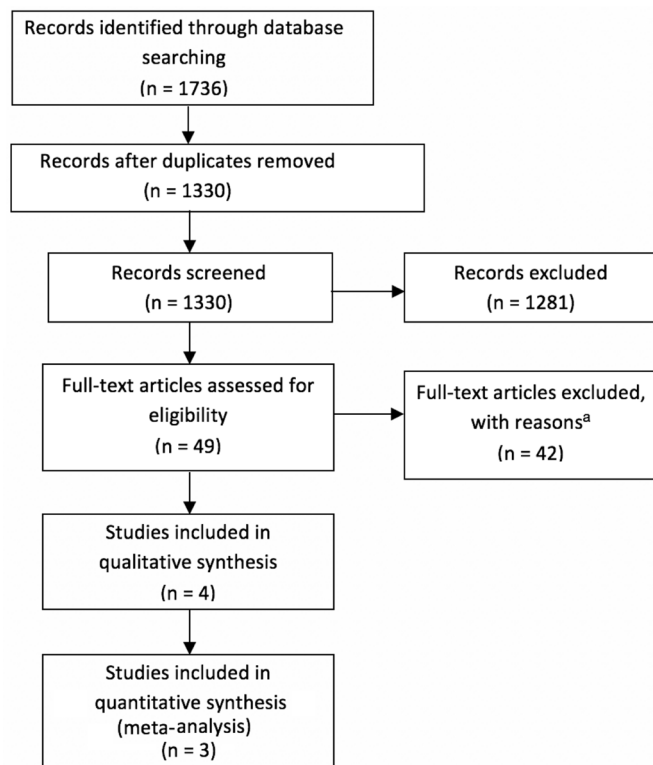

Figure 1 Flow diagram of studies included in this Meta-analysis
[a]Studies had less than one year of follow up; trials of different doses of aflibercept compared to each other, with no control or comparator; studies used aflibercept in combination with other treatments; reviews.

Figure 2 Risk of bias of included studies.

assigned 660 patients with DMO to be treated with intravitreal aflibercept (2.0 mg dose, 224 patients), bevacizumab (1.25 mg, 218), or ranibizumab (0.3 mg, 218). The injections were carried out as often as every 4wk according to an algorithm.

Efficacy Analysis Patients receiving intravitreal aflibercept were more likely to gain 3 or more lines of visual acuity (VA) over 1y or 2y compared to patients treated with photocoagulation (RR=3.81, 95%CI 2.61 to 5.56, 661 patients, 3 studies, $P<0.00001$, $I^2=0$; RR=2.56, 95%CI 1.80 to 3.62, 572 patients, 2 studies, $P<0.00001$, $I^2=0$, respectively; Figure 3).

Those receiving aflibercept were also less likely to lose 3 or more lines of VA over 1 or 2y (RR=0.06, 95%CI 0.01 to 0.23, 661 patients, 3 studies, $P<0.0001$, $I^2=0$; RR=0.09, 95%CI 0.03 to 0.30, 572 patients, 2 studies, $P<0.0001$, $I^2=0$, respectively; Figure 4).

Two studies involving 572 patients compared aflibercept with photocoagulation in regards to mean change in BCVA at 1y or 2y from baseline. The combined results demonstrated that aflibercept produced significantly greater improvement in BCVA at 1y or 2y (weighted mean difference =10.01, 95%CI 8.32 to 11.69, $P<0.00001$, $I^2=0$; weighted mean difference =9.42, 95%CI 7.49 to 11.35, $P<0.00001$, $I^2=0$, respectively; Figure 5).

The combined results also demonstrated that aflibercept was more efficacious in reducing CMT at 1y or 2y (weighted mean difference =119.02, 95%CI 95.47 to 142.57, 661 patients, 3 studies, $P<0.00001$, $I^2=0$; weighted mean difference=108.80, 95%CI 83.20 to 134.40, 572 patients, 2 studies, $P<0.00001$, $I^2=0$, respectively; Figure 6).

Eyes treated with intravitreal aflibercept in the VISTA and VIVID trials demonstrated significantly greater improvements in visual and anatomic outcomes compared with eyes treated with photocoagulation at 1 and 2y. The improvements observed at 2y in mean baseline BCVA and CMT, and proportion that gained 3 or more lines of VA, were maintained over 148wk of treatment.
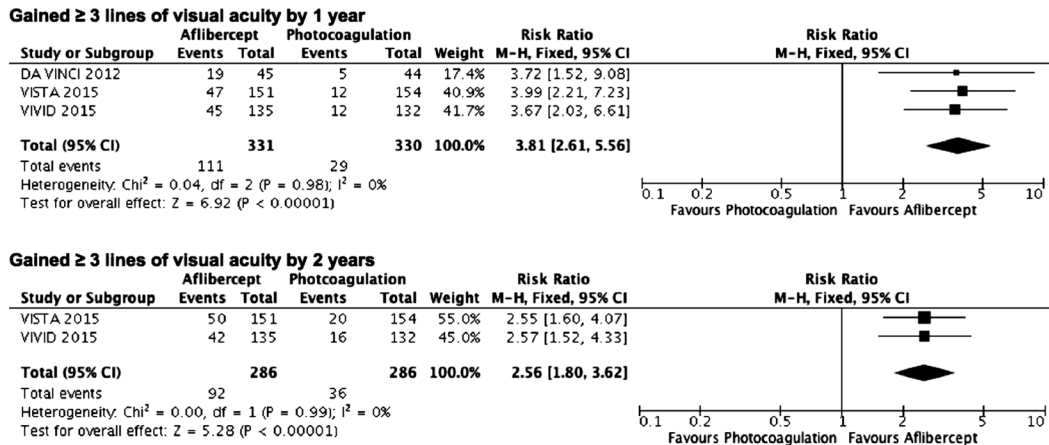
Figure 3 Estimated risk ratios of gains of 3 or more lines of visual acuity from baseline as measured on a logMAR chart M-H: Mantel-Haenszel statistics.
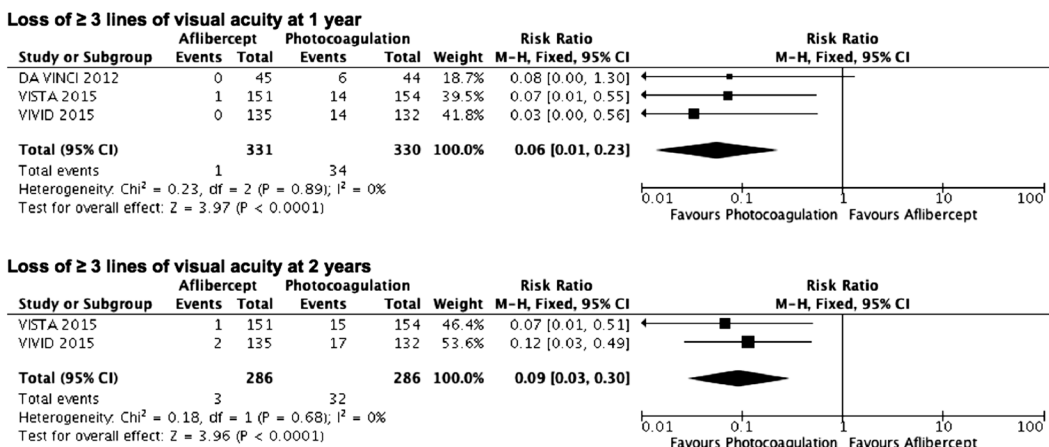

Figure 4 Estimated risk ratios of loss of 3 or more lines of visual acuity from baseline as measured on a logMAR chart M-H: Mantel-Haenszel statistics.
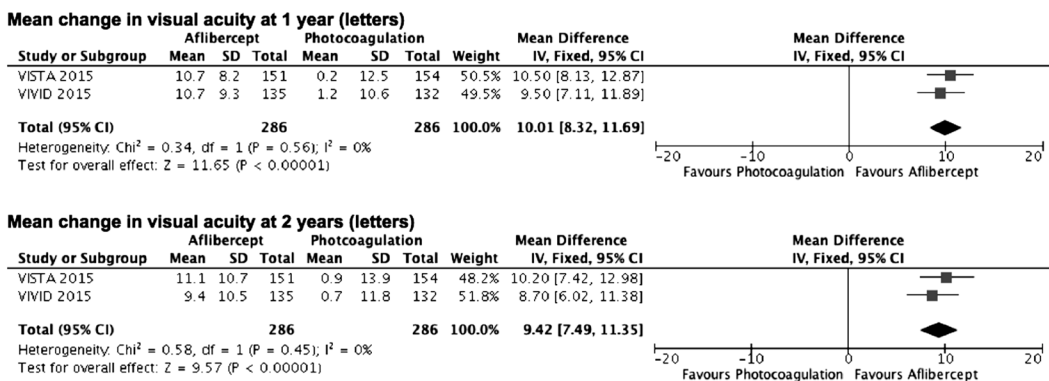

Figure 5 Estimated mean difference in changes from baseline to follow up best corrected visual acuity (in letters) IV: Inverse variance; SD: Standard deviation.

In patients with worse baseline VA letter score (VA letter score of less than 69, Snellen equivalent 20/50 or worse) in the DRCRN trial, aflibercept was superior to bevacizumab and ranibizumab at improving 15 or more letters at one-year follow up (*P*<0.001 and *P*=0.008, respectively). However, in patients with better baseline VA (VA letter score 78 to 69, Snellen equivalent 20/32 to 20/40), there were no significant differences in the gain or loss of 15 or more letters between

the anti-VEGF agents at one-year follow up. There were no statistically significant differences between the anti-VEGF agents for patients with at least 15-letter changes at the two-year follow up.

In the DRCRN trial at one-year follow up, in patients with worse baseline VA, the mean difference in BCVA was 6.5 (95%CI 2.9 to 10.1, *P*<0.001), and 4.7 letters (95%CI 1.4 to 8.0, *P*=0.003) for aflibercept versus bevacizumab, and
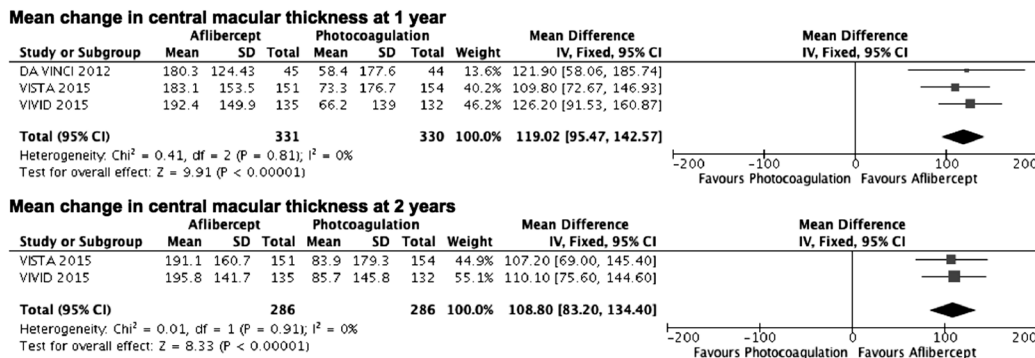
Figure 6 Estimated mean difference in changes from baseline to follow up central macular thickness IV: Inverse variance; SD: Standard deviation.
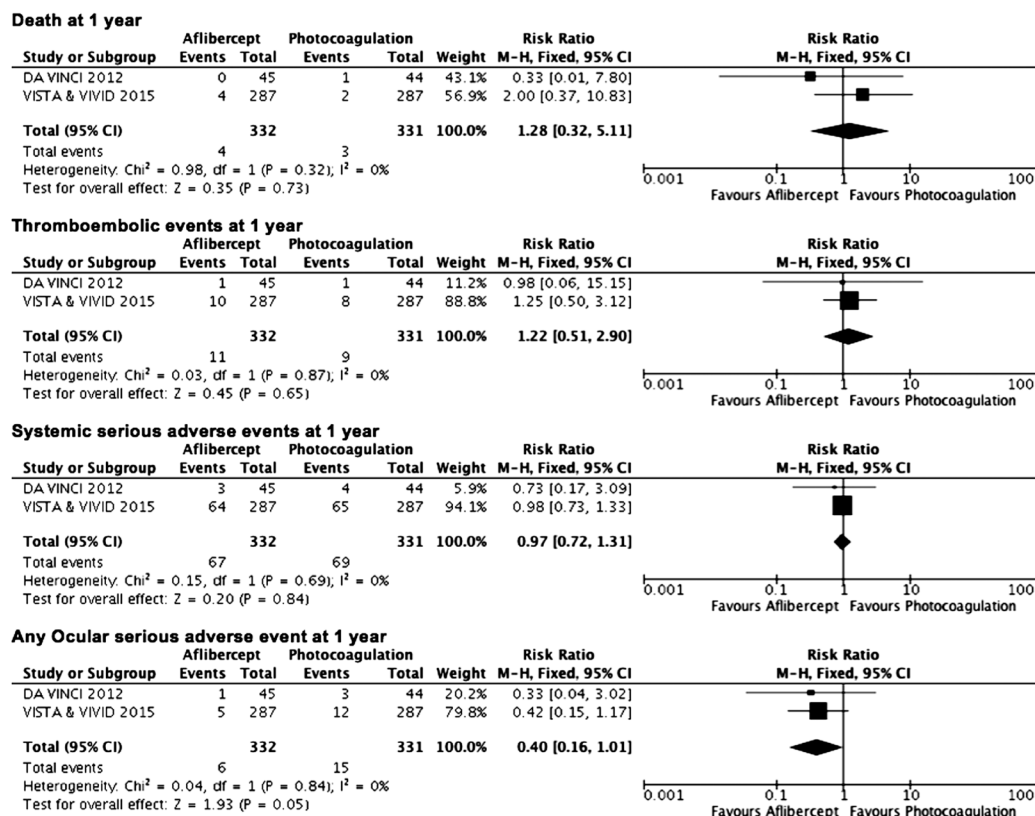

Figure 7 Estimated relative risks of serious adverse events M-H: Mantel-Haenszel statistics.

aflibercept versus ranibizumab respectively. At two-years follow up, in patients with worse baseline VA, there remained a significant difference between aflibercept versus bevacizumab, with aflibercept providing superior mean change in BCVA (mean difference =4.7, 95%CI 0.5 to 8.8, P=0.02).

After two-years of treatment, aflibercept provided superior reduction in CMT overall compared to bevacizumab (mean difference =48.5, 95%CI 27 to 70, P<0.001) and ranibizumab (mean difference =15.5, 95% CI 2.0 to 33.0, P=0.08).

Safety Analysis There were no significant differences between aflibercept and photocoagulation with respect to death, thromboembolic events, systemic serious adverse events or any ocular serious adverse events at 1y. There was no statistical heterogeneity detected between the studies (Figure 7).

Similarly, at 2y, combined data from two trials did not demonstrate significant differences between aflibercept and photocoagulation. No new safety concerns were demonstrated in the VISTA and VIVID trials with a longer treatment period of 148wk.

In the DRCRN trial, there were no significant differences with aflibercept when compared to bevacizumab or ranibizumab in rates of death, any systemic serious adverse event, or any ocular serious adverse event. At two-year follow up, the higher rate of Antiplatelet Trialists' Collaboration (APTC) thromboembolic events for ranibizumab included more non-fatal strokes (11 for ranibizumab, 6 for bevacizumab, and 2 for aflibercept) and vascular deaths (9 for ranibizumab, 8 for bevacizumab, and 3 for aflibercept). This was significant when aflibercept was compared to ranibizumab (P=0.047).

DISCUSSION

Four RCTs were reviewed, with 3 RCTs (331 patients in the aflibercept group and 330 patients in the photocoagulation group) included in the Meta-analysis. In terms of efficacy, patients receiving aflibercept were more likely to gain 3 or more lines of VA, and less likely to lose 3 or more lines of VA over one year or two years. In addition, intravitreal aflibercept demonstrated greater efficacy in terms of effect on improvement in mean BCVA and reduction in mean CMT when compared to photocoagulation at 1 or 2y. In terms of safety, rates of death, thromboembolic events, any systemic serious adverse event or any ocular serious adverse event at 1 or 2y were similar with aflibercept and photocoagulation. Intravitreal aflibercept treatment provided visual and anatomic improvements as well as comparable safety through to week 148 of treatment[26].

There was high quality evidence that aflibercept provides superior benefit compared to laser photocoagulation in combined clinical trial populations at one or two years. Nevertheless, the conditions in clinical trials are highly controlled and the patients may not be representative of the real-world population with DMO. Studies assessing the real-world effectiveness of aflibercept for DMO would be of benefit to determine whether the results of clinical trials translate to real-world conditions.

Treatment of DMO with anti-VEGF agents is now established. As well as the need to investigate real-world effects, future research should compare different anti-VEGF agents and treatment regimens. Differences among anti-VEGF agents were evaluated in only one high quality trial comparing aflibercept to bevacizumab and ranibizumab. The DRCRN trial compared treatment with intravitreal aflibercept, bevacizumab, or ranibizumab in eyes with centre-involving DMO and found some differences between the anti-VEGF agents in terms of efficacy and safety[18-19]. At one-year follow up aflibercept demonstrated greater improvement in VA compared to ranibizumab and bevacizumab amongst patients with poorer levels of baseline VA. Although the superiority of aflibercept over bevacizumab for VA improvement for these patients persisted through 2y, the difference between aflibercept and ranibizumab seen at year one did not persist.

The lack of other comparative effectiveness trials between aflibercept and other anti-VEGF agents did not allow for this Meta-analysis. Further RCTs comparing aflibercept to other anti-VEGF agents will be of benefit to ophthalmologists and patients when deciding between treatment options. Comparison of aflibercept with bevacizumab and ranibizumab in regards to safety profile will also be important as higher APTC thromboembolic events were seen with ranibizumab[19]. This review has limitations in that publication bias could not be fully eliminated. Nevertheless, the findings indicate that aflibercept offers greater benefits in terms of improving and maintaining vision when compared to photocoagulation. This Meta-analysis also demonstrates the safety of aflibercept to treat DMO; there were no differences between aflibercept and photocoagulation in terms of rates of death, thromboembolic events, any serious systemic adverse event, or any serious ocular adverse event at 1 or 2y.

This Meta-analysis confirms the comparable safety and superior efficacy of aflibercept over photocoagulation for patients with DMO. It also highlights the need for further comparative trials of anti-VEGF agents and investigations assessing treatment effects in the real world.

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