Original Article

Efficacy of switching therapy to aflibercept for patients with persistent diabetic macular edema: a systematic review and meta-analysis

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Background: To evaluate functional and anatomical consequences of switching anti-vascular endothelial growth factor (anti-VEGF) therapy from bevacizumab and/or ranibizumab to aflibercept intravitreal injection for the treatment of persistent diabetic macular edema (DME).

Methods: Analysis of switching treatment in patients with persistent DME was performed using a literature search across multiple databases (PubMed, Medline, EMBASE, Cochrane Library and Web of Science) prior to May 2019. Therapeutic effect parameters, including mean change of best-corrected visual acuity (BCVA) and central macular thickness (CMT), were extracted from baseline to different follow-up times post initial injections. The quality of studies was assessed with the Downs and Black checklist. Data pertaining to ocular and systemic safety adverse events (SAEs) were collected as well as subgroup analysis stratified by pre-switch anti-VEGF reagents. All results were analyzed and pooled using random-effects models with 95% confidence intervals (CI).

Results: Fourteen studies involving 489 eyes met the inclusion criteria. The mean differences in BCVA were significantly improved at 1, 2 and 3 months with −0.11 logMAR (P=0.016), −0.22 logMAR (P<0.001) and −0.24 logMAR (P<0.01), respectively. Vision gain was also assessed following the aflibercept injection with a mean change of −0.10 logMAR (P<0.001) at 6 months and −0.08 logMAR (P=0.01) at 12 months. CMT reduction was significant from baseline with a mean decrease of 80.52 μm (P<0.001) at 1 month, 89.6 μm (P<0.013) at 2 months, 113.88 μm (P<0.001) at 3 months and 125.12 μm (P<0.001) at 6 months. Mean CMT continued to decline by 75.70 μm (P<0.001) at 12 months as well.

Conclusions: This meta-analysis indicated the comparable efficacy and safety of a conversion treatment to aflibercept in cases of unsatisfactory responses to other anti-VEGF drugs. Switching treatment produces significant advantage for vision acuity recovery and macular edema improvement among persistent DME patients.

Keywords: Aflibercept; anti-vascular endothelial growth factor; diabetic macular edema (DME); switching treatment

Submitted Sep 14, 2019. Accepted for publication Jan 10, 2020.
doi: 10.21037/atm.2020.02.04
View this article at: http://dx.doi.org/10.21037/atm.2020.02.04

Introduction

Diabetic macular edema (DME), a sight-threatening complication of diabetic retinopathy (DR), is clinically characterized by retinal thickening of extracellular fluid exudation and accumulation in the macula area secondary to abnormal vascular permeability (1). Global prevalence of DME is 6.81% and the number of DME patients was approximately 20.6 million in 2010 (2).

Vascular endothelial growth factor (VEGF) has been demonstrated to be a pivotal mediator that contributes to the pathogenesis of DME (3,4). In recent years, anti-vascular endothelial growth factor (anti-VEGF) drugs have become first-line treatment for DME, showing beneficial vision gain and control of disease progression (5). However, some patients failed a response to intravitreal bevacizumab (IVB) or ranibizumab (IVR) after a minimum of three injections treatment (6-8) and may develop persistent fluid re-accumulation and neuronal damage within the retina, leading to visual impairment and limited vision recovery (9).

It is suggested that a conversion treatment to a latest anti-VEGF drug, aflibercept, could improve chronic macular edema and provide long-term vision benefits. Compared to bevacizumab and ranibizumab, aflibercept substantially has multiple targets, higher binding affinity to VEGF-A and additionally inhibits placental growth factor and VEGF-B (10).

Several clinical trials have suggested that DME patients with incomplete response to previous anti-VEGF injections may benefit from an alternative anti-VEGF therapy, showing superiority of aflibercept over bevacizumab or ranibizumab (11-13). Pharmacologic conversion represents a promising strategy for treating resistant DME, yet the efficacy of this treatment has not been evaluated comprehensively.

To address this gap in knowledge, we performed a systematic meta-analysis to investigate the outcomes of visual and retinal anatomical changes among DME refractory patients following conversion to aflibercept therapy.

Methods

Literature search

A computational search was performed to collect relevant studies across five databases (PubMed, Medline, EMBASE, Cochrane Library and Web of Science) prior to May 30. The search strategy was carried out using the Medical Subject Headings and keywords “diabetic macular edema or DME” with “aflibercept”, as well as any of the following words: “resistant”, “refractory”, “recalcitrant”, “conversion”, “switching” and “non-response”. Studies published in English reporting a switch from one anti-VEGF drug (bevacizumab or ranibizumab) to aflibercept in longstanding DME were collected and all date ranges available in the databases were included.

Eligibility criteria

Clinical trials that met the following criteria were deemed eligible: (I) patients over 18 years of age with persistent DME who had switched to aflibercept from previous unresponsive anti-VEGF therapy (bevacizumab or/and ranibizumab); (II) studies that provided both main outcome evaluation parameters as mean ± SD: best-corrected visual acuity (BCVA) and central macular thickness (CMT); (III) all randomized controlled trials (RCTs), cohort studies, and retrospective studies with full-text articles; (IV) all included studies should be compliant with the Declaration of Helsinki and written informed consent from enrolled patients. Conference abstract, letters without data, reviews and case reports with fewer than five cases were excluded. If the same study subjects were reported in different publications, only the most recent publication was included.

Data extraction and quality assessment

Assessment of full-text articles and data extraction from each study was independently conducted by two authors (YL and JH), including publication metrics (name of the first author, year of publication, location and study design), demographic characteristics (number of eyes and mean age), treatment information (pre-switch and post-switch injection numbers, type of anti-VEGF drug, injection intervals), duration of follow-up and treatment outcomes corresponding to BCVA and CMT. If studies have missing data in terms of mean and standard deviation (SD) in BCVA and CMT parameters but provided each patient’s original vision and CMT records, we primarily calculated the mean and SD data and then acquired the paired difference based on The Cochrane Handbook (14) of the following formula:

$$SD_{paired difference} = \sqrt{[(SD_1)^2+(SD_2)^2-2 \times r \times SD_1 \times SD_2]}.$$

SD_1 = standard deviation of the pre-treatment value, SD_2 = standard deviation of the post-treatment value, r = correlation coefficient. We set r =0.4 as correlation coefficient.

The methodological quality assessment of selected

studies was measured using criteria from a modified version of the Downs and Black checklist (15) independently by two independent reviewers. The tool is appropriate for both randomized and non-randomized studies with total scores ranging from 0 to 28. Consequently, higher scores indicated lower risk of bias and studies scored less than 15 were excluded in this meta-analysis. To aid in interpretation of different scores, we classified study quality and risk of bias as follows: poor quality [0–14], high risk of bias; fair quality [15–19], moderate risk of bias and high quality [20–28], low risk of bias. All studies were assessed as fair quality, moderate risk of bias. Any conflicting evaluations or disparities were resolved through discussion and consensus.

Evaluation indicators

Vision-related outcomes of treatment efficacy included mean changes in BCVA and CMT, from pre-switch baseline to different post-switch endpoints. When BCVA data was presented in Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores or Snellen acuity fraction, it was transposed to logarithm of the minimum angle of resolution (log MAR) units (15). Safety indicators included systemic or ocular safety adverse events during the injection treatment.

Statistical analysis

We analyzed the quantitative evidence with STATA version 12.0 (STATA corporation, college station, TX). Continuous data were expressed as means and standard deviations, and weighted mean differences (WMD) were calculated. Besides, they were recorded as mean differences with corresponding 95% confidence intervals (CIs). Heterogeneity variances were estimated by means of a standard χ^2-based Cochran's Q test along with the I^2 statistic, measuring the percentage of variability that cannot be attributed to random error. P<0.1 and I^2 ≥50% indicates a considerable level of heterogeneity. Random-effect models were used to pool the data since the interventions varied among included studies (16). Potential publication bias was assessed by Begg's and Egger's test and funnel plots with P>0.05 indicating negative publication bias. One-way sensitivity analysis was performed to detect the stability of outcomes using the leave-one out approach. Statistical significance was determined using the two-tailed test, where P values less than 0.05 were defined as significant.

Results

Description of studies

A total of 38 studies were initially identified by the search terms prior to May 2019, of which 13 studies were excluded as reviews or letters and 6 studies were removed manually after skimming through the titles or abstracts. Additionally, two articles reported the same trial at different time points, so we kept the most recent one. Among the remaining 19 trials, 5 articles were rejected due to the eligibility criteria. Of the 14 studies, there were 5 prospective studies and 9 retrospective studies finally included for meta-analysis (*Table 1*), and all available studies met the eligibility standards described above. The literature selection process and reasons for exclusion are summarized in (*Figure 1*).

Baseline characteristics

Basic information and quality assessment scores for the 14 studies are listed in *Table 1 and Table S1*. Overall, sample sizes varied from 11 to 72 eyes, with a total of 489 eyes included in the analyses and the duration of follow-up time ranged from 1 to 24 months. Mean age and HbA1c levels of all the patients ranged from 56.07 to 70.3 years old and 6.9% to 8.0%, respectively. The mean baseline BCVA logMAR scores ranged from 0.33 to 0.87 and mean CMT ranged from 324.0 to 501.47 μm. Eyes received a mean number of anti-VEGF injections pre-switch ranged from 4.3 to 21.1. Injection numbers differed in the post-switch aflibercept treatment, but most trials used pro re nata (PRN) dosing after 3 monthly regular doses.

Best-corrected visual acuity

BCVA data was selected as an essential visual outcome parameter to evaluate the switch treatment efficacy. The mean change in BCVA of each study was assessed from baseline to several post-switch endpoints using forest plots. Six studies, with a total of 216, eyes were included in comparison of BCVA changes from baseline to the first month after conversion therapy. The pooled results revealed a visual acuity improvement in BCVA from baseline with a mean increase of −0.11 logMAR (95% CI, −0.20 to −0.02 logMAR, P=0.016; *Figure 2A*). In the three studies (n=80 eyes) with 2 months of follow-up, significant changes can be confirmed in the evaluation of BCVA from baseline with a mean increase of −0.22 logMAR (95% CI, −0.32 to −0.12 logMAR, P<0.001; *Figure 2B*). BCVA improvement

Table 1 Study characteristics of the fourteen trials in the meta-analysis

Authors	Year	Location	Study design (data collection)	Sample eyes [patients]	Anti-VEGF type before switching	Age (y); mean ± SD [range]	HbA1c levels (%)	Follow-up (mo)	Number of injections prior to switch [range]	Mean number of aflibercept injections [range]	Downs & Black Score
Herbaut *et al.* (17)	2017	France	Self control (retrospective)	23	IVR	63.1±10.8	8.3 (7.5–10.7)	3, 6	9±4.6 [3–15]	3+PRN	17
Bahrami *et al.* (12)	2019	Australia	Self control (prospective)	41 [41]	IVB	62.9±9.7	8.0±1.7	24 and 48	16.6±11.5	8	16
McCloskey *et al.* (6)	2018	Ireland	Self control (retrospective)	18 [13]	IVB or/and IVR	68±6.6	N/A	6	IVB: 7±5.6; IVR: 4.3±4.4	8.4±3.9	17
Nixon *et al.* (18)	2018	Canada	Self control (prospective)	50 [40]	IVR	70.3±11.3	N/A	20 weeks	21.1±11.9 [5–55]	5	17
Wood *et al.* (8)	2015	USA	Self control (prospective)	14	IVB or/and IVR	N/A	N/A	3	5.3	1	15
Rahimy *et al.* (11)	2016	USA	Self control (retrospective)	50 [37]	IVB or/and IVR	69.9±9.4	7.0±0.9	4.6 [2–9]	13.7±6.1 [4–30]	4.1±1.7 [2–9]	16
Konidaris *et al.* (19)	2017	UK	Self control (prospective)	49 [49]	IVR	67.48±11.4	N/A	24 weeks	6.3	2.58 [2–4]	15
Mira *et al.* (20)	2017	Portugal	Self control (retrospective)	32 [26]	IVR	65.59±10.30	N/A	3	5.34±2.38	2.0±0.0	18
Klein *et al.* (7)	2017	USA	Self control (retrospective)	11	IVB or/and IVR	65 [47–83]	7.2±1.1	6	4.3 [3–6]	4.7 [4–6]	15
Lim *et al.* (21)	2015	USA	Self control (retrospective)	21 [19]	IVB or/and IVR	62.0±15.0	6.9±0.7	5	N/A	N/A	16
Ashraf *et al.* (22)	2017	Egypt	Self control (retrospective)	17 [14]	IVB	56.07±8.10	N/A	1	5.76±3.52	1	16
Laiginhas *et al.* (23)	2018	Portugal	Self control (retrospective)	49 [34]	IVB	65.8±8.8	7.3±1.0	2.4±2.1	N/A	2.2±0.9	15
Ibrahim *et al.* (24)	2019	Egypt	Self control (prospective)	42 [42]	IVB or/and IVR	60.04±6.89	7.32±0.55	3	6.33±1.15	3	17
Chen *et al.* (13)	2017	China	Self control (retrospective)	72 [72]	IVB or IVR	58.6±7.2	7.7±1.2	3	IVB: 7.2±3.4; IVR: 5.7±2.1	3	17

IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; N/A, not available; SD, standard deviation; VEGF, vascular endothelial growth factor.

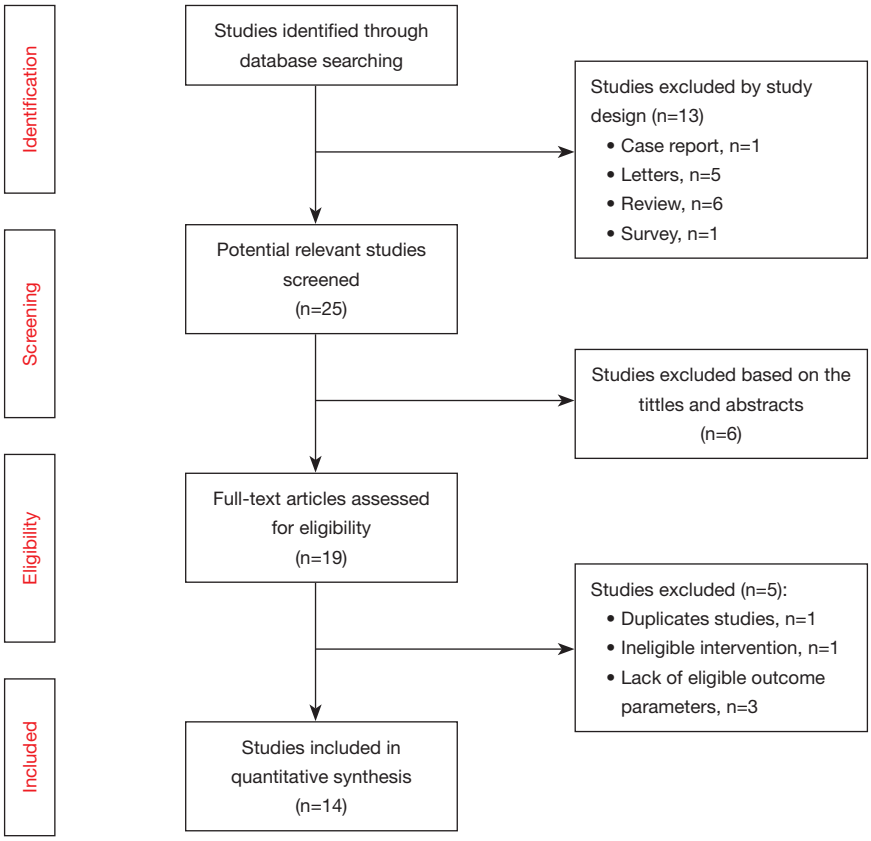

Figure 1 PRISMA flow diagram of study identification process.

was analyzed in five studies from baseline to 3 months after aflibercept injection. The pool mean improvement was −0.24 logMAR (95% CI, −0.42 to −0.06 logMAR, P<0.01; *Figure 2C*) for 219 eyes. However, the results indicated a significant difference in BCVA post-aflibercept switch at 5 months follow-up between two studies, while results fluctuated when we analyzed the data with a mean change of −0.05 logMAR (95% CI, −0.10 to −0.00 logMAR, P=0.052). At 6 and 12 months, BCVA significantly improved by a mean of −0.10 logMAR (n=142, 95% CI, −0.14 to −0.05 logMAR, P<0.001; *Figure 2D*) and −0.08 logMAR (n=59, 95% CI, −0.13 to −0.02 logMAR, P=0.01; *Figure 2E*), respectively. There was no significant heterogeneity found among the 5 studies at 6 months (I^2 =0%, P=0.54). Likewise, no statistical evidence indicated heterogeneity between 2 studies at the 12-month time point (I^2 =8.2%, P=0.30).

Central macular thickness

The progress of anatomical outcome of each study from baseline to different follow-up time is shown in *Figure 3*.

One month following the switch of anti-VEGF, CMT of 216 patients in six studies declined with a mean of 80.52 μm (95% CI, −109.34 to −51.70 μm, P<0.001; *Figure 3A*). Three studies were included in the assessment of CMT between baseline and 2 months, with a mean reduction of 89.6 μm (95% CI, −160.41 to −18.78 μm, P<0.013; *Figure 3B*). Reduction of CMT was reported at 3-month time point in five studies, demonstrating a mean decrease of 113.88 μm (95% CI, −156.72 to −71.04 μm, P<0.001; *Figure 3C*). Results from two studies indicated a significant difference at 5 months whereas the results fluctuated through the analysis (95% CI, −170.22 to 14.01 μm, P=0.09). Six studies at month 6 and 12 studies at month 12 were analyzed in the assessment of CMT outcomes as well, which reduced with a mean of 125.12 μm (95% CI, −185.32 to −64.92 μm, P<0.001; *Figure 3D*) and 75.70 μm (95% CI, −114.92 to −36.48 μm, P<0.001; *Figure 3E*), respectively.

Subgroup analysis

Classification of different anti-VEGFs (IVB, IVR, IVB or/

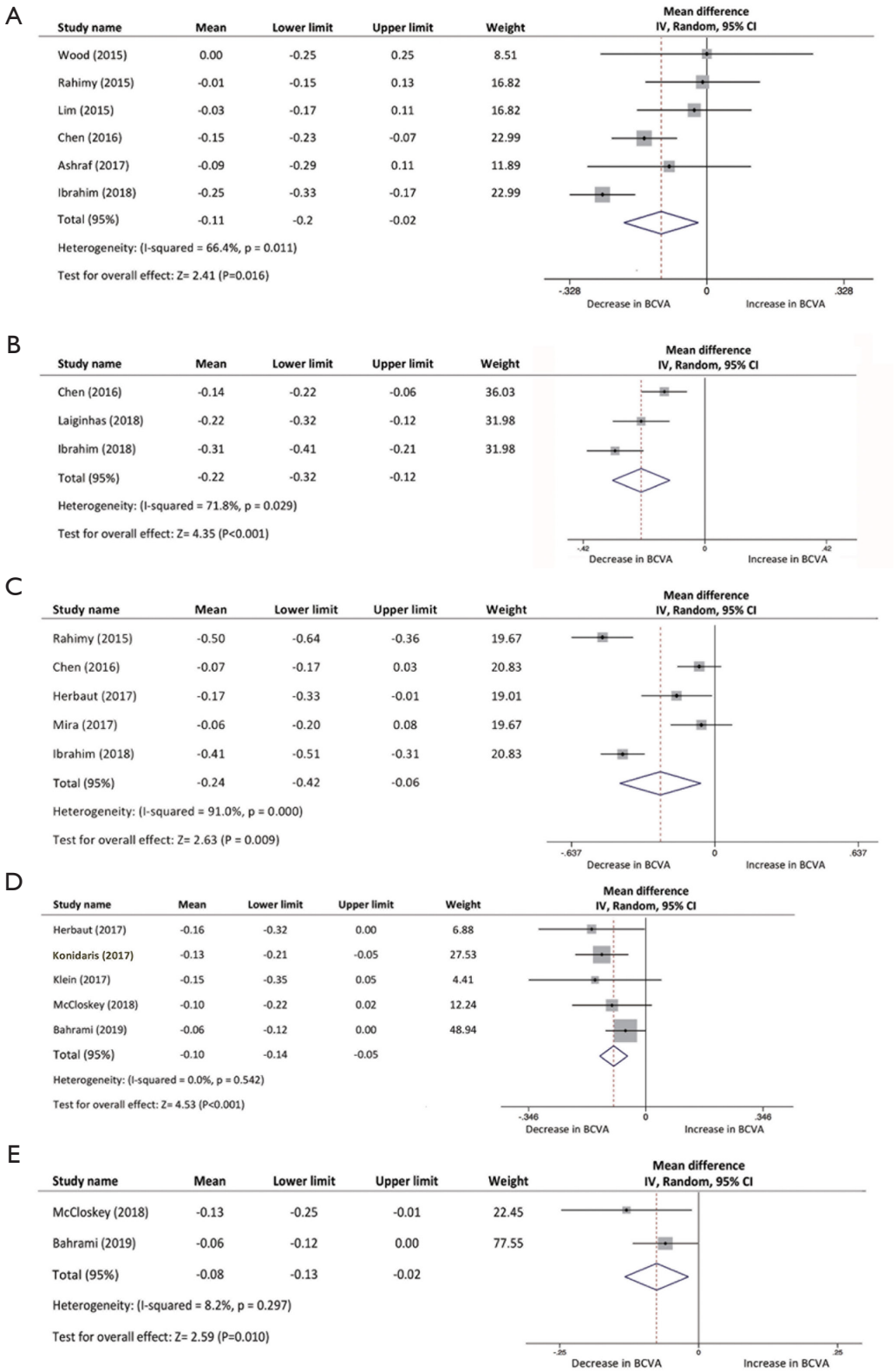

Figure 2 Forest plot of each study with mean change of best-corrected visual acuity (BCVA, logMAR) from baseline to different follow-up times after switching to aflibercept. (A) 1 month; (B) 2 months; (C) 3 months; (D) 6 months; (E) 12 months.

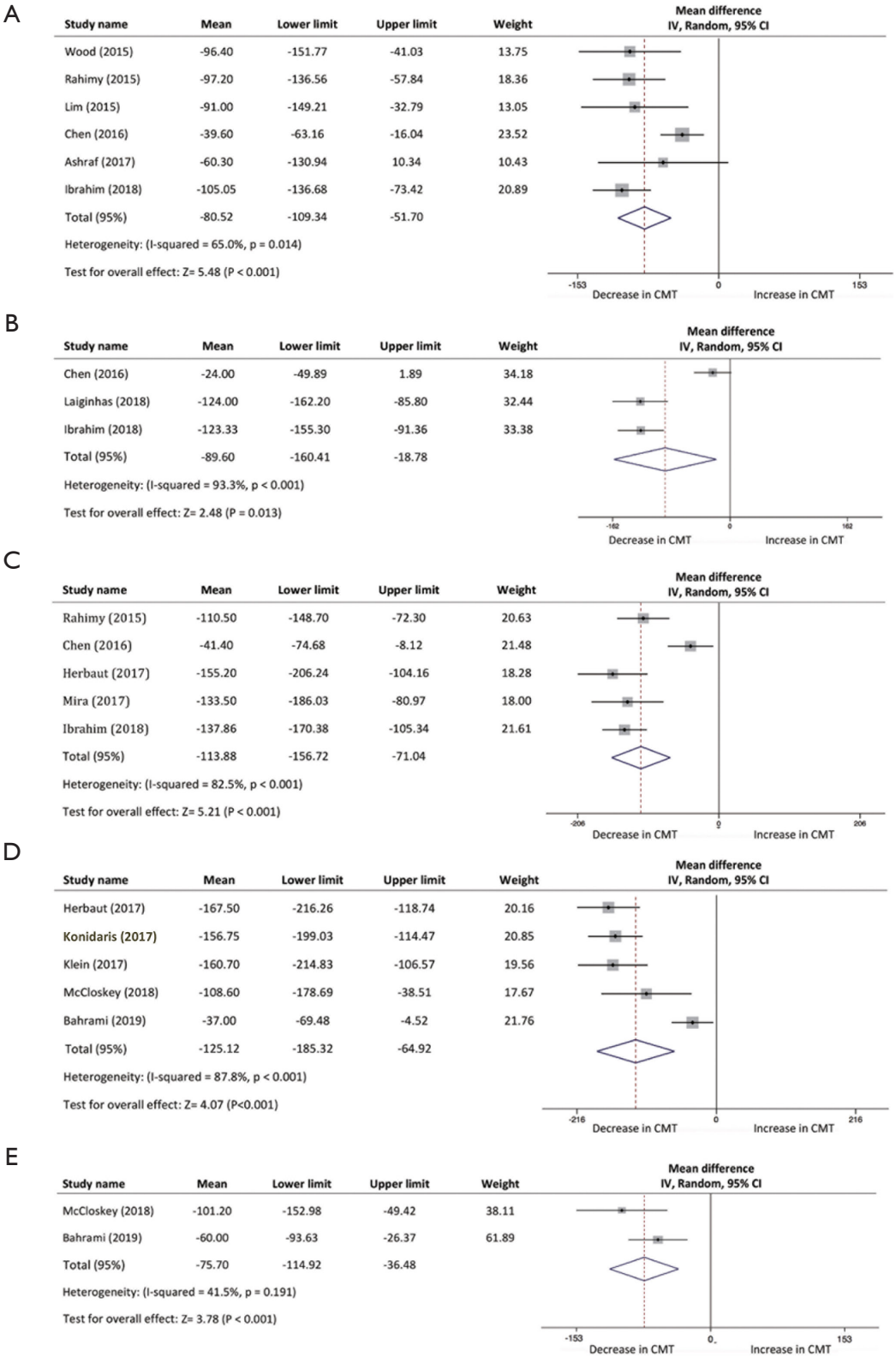

Figure 3 Forest plot of each study with mean change of central macular thickness (CMT, μm) from baseline to different follow-up times after switching to aflibercept. (A) 1 month; (B) 2 months; (C) 3 months; (D) 6 months; (E) 12 months.

Table 2 Subgroup analysis of BCVA and CMT outcomes according to pre-switch reagents (mean and 95% confidence intervals)

	IVR	IVB	IVR and/or IVB
BCVA 1 month (logMAR)	N/A	−0.09 (−0.29 to −0.11)	−0.11 (−0.21 to −0.01)
BCVA 3 month (logMAR)	−0.11 (−0.22 to −0.00)	N/A	−0.32 (−0.58 to −0.06)
BCVA 6 month (logMAR)	−0.14 (−0.21 to −0.07)	−0.06 (−0.12 to −0.00)	−0.11 (−0.21 to −0.01)
CMT 1 month (μm)	N/A	−60.30 (−130.94 to 10.34)	−83.24 (−115.57 to −50.92)
CMT 3 month (μm)	−144.66 (−181.27 to −108.06)	N/A	−96.50 (−155.15 to −37.85)
CMT 6 month (μm)	−161.36 (−193.31 to −129.42)	−37.00 (−69.48 to −4.52)	−139.60 (−189.73 to −89.47)

BCVA, best-corrected visual acuity; CMT, central macular thickness; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; logMAR, logarithm of the minimum angle of resolution; N/A, not available.

and IVR) before the switching treatment was subjected to subgroup analysis. Due to the limitation of study number, only three follow-up time points were included (*Table 2*). BCVA changes between IVB or/and IVR subgroup and IVB subgroup were comparable. The former subgroup demonstrated a greater visual improvement, while IVB subgroup was observed no significant gain at 1 month (−0.09 logMAR, 95% CI, −0.29 to −0.11 logMAR, P=0.368; *Figure S1*) and a slight mean change at 6 months (−0.06 logMAR, 95% CI, −0.12 to −0.00 logMAR, P=0.046; *Figure S1*), respectively.

The mean reduction of CMT in pre-switch IVR treatment subgroup was measured at 3 months (144.66 μm, 95% CI, −181.27 to −108.06 μm, P<0.001; *Figure S2*) and 6 months (161.36 μm, 95% CI, −193.31 to −129.42 μm, P<0.001; *Figure S2*), greater than other two subgroups. Moreover, the pool results revealed a better mean CMT decrease in IVR or/and IVB group at 1 month (83.24 μm, 95% CI: −115.57 to −50.92 μm, P<0.001; *Figure S2*) and 6 months (139.60 μm, 95% CI: −189.73 to −89.47 μm, P<0.001; *Figure S2*) when compared to IVB group (60.30 μm, 95% CI: −130.94 to 10.34 μm, P=0.094; *Figure S2*) and (37.00 μm, 95% CI: −69.48 to −4.52 μm, P=0.026; *Figure S2*), respectively.

Publication bias

All studies were deemed to exhibit no publication bias when analyzed from visual inspection of the funnel plots and by Begg's test (P=0.343 BCVA and P=0.546 CMT), but possible bias evidence was tested by Egger's test (P=0.343 BCVA and P=0.031 CMT). Strong evidence of possible inter-study heterogeneity was observed in the overall pooling of all eligible studies in both BCVA (I^2 =84.1%, P<0.001) and CMT.

Safety

Instances of safety adverse events (SAEs) were few among all studies and no significant heterogeneity was tested. Of the 14 trials, 9 studies reported no severe SAEs and 4 studies showed no safety data during the treatment. Despite some typical side effects associated with intravitreal injections, such as subconjunctival hemorrhage, severe ocular SAEs were minimal with only 1 study recording a patient with rhegmatogenous retinal detachment. Twelve significant systemic SAEs (myocardial infraction, etc.) were reported in one study during the follow-up period (12). Whether these events are drug-related issues remains unclear.

Discussion

Diabetic macular edema is reportedly the most common manifestation of DR, which can cause vision impairment in patients with diabetes. Notably, injections of anti-VEGF reagents have become the standard treatment worldwide in DME patients (25).

However, DME chronically persists in a portion of patients, who somehow suffered from suboptimal or worsening responses to bevacizumab or ranibizumab. Lack of response to these therapies can be attributed to the phenomenon known as tachyphylaxis or tolerance (26,27). Preliminary studies suggested a decreased bioefficacy in AMD patients after repeated IVB (28).

To address these patients, a novel therapeutic option, switching to aflibercept, has been used in limited trials, demonstrating potential benefit among patients with unsatisfactory responses to initial anti-VEGF drugs. One

study (29) reported 10 patients with polypoidal choroidal vasculopathy (PCV) who developed tachyphylaxis to ranibizumab injections and suggested that the switching treatment was effective. Nevertheless, whether there was promising improvement after aflibercept injection or the feasibility of the conversion method in DME patients, needed to be assessed.

To the best of our knowledge, this is the first meta-analysis study that assessed the efficacy and safety of aflibercept retreatment in DME patients with other anti-VEGF treatment failure.

In this meta-analysis, we examined 14 studies representing 489 eyes based on robust search method and precisely data extraction following a systematic review process. Based on the studies enrolled in this meta-analysis, most of the articles reported significant changes in BCVA and CMT parameters, which is in consistent with our overall results. Our analysis showed that DME patients could obtain significant visual improvement in BCVA as well as the anatomic reduction of CMT at 1, 2, 3, 6 and 12 months. Due to the limited data, it was impossible to evaluate treatment efficacy at longer time points.

The increased response in recalcitrant DME patients might reflect the particular pharmacologic profile of aflibercept. Among anti-VEGF drugs, only aflibercept can inhibit both placental growth factor (PGF) and VEGF, which are key factors contributing to the pathogenesis of DR or DME. More importantly, aflibercept is featured with faster association rate (77- and 256-fold faster than bevacizumab and ranibizumab, respectively) and higher binding affinity (about 100-fold higher) over other reagents yielding a doubling of VEGF blockade time (30). And then after the injection of active aflibercept fusion protein followed by new interaction with multiple inflammatory targets, the recurrent edema in a number of DME patients may be optimized due to the theoretical advantages of aflibercept.

Of note, patients in three studies (8,11,31) were observed without significant gains in visual outcomes at the first month follow-up. One possible explanation is that those patients may require a longer-term regimen to reach a favorable effect. Since macular edema has caused persisting retinal damage, sustained treatment might be required for significant results. Another reason can be explained by the multifactorial etiology of DME. Anti-VEGF drugs are not functional for every inflammatory mediator involved in the pathological process, so other therapies or combination treatments need to be evaluated or discovered.

Subgroup analysis by different anti-VEGF agents administered pre-switch was conducted and the outcomes appeared to show different response rates between switching drugs. In contrast, patients who were given bevacizumab and/or ranibizumab treatment before were trended to obtain a better visual acuity and edema reduction than those with only bevacizumab injections. Additionally, non-responders with only ranibizumab injections presented greater morphological parameters than other two groups.

This meta-analysis contains some limitations. First of all, publication bias could not be excluded, which can be tested in the appraisal of both BCVA and CMT outcomes. The indication of the inter-study heterogeneity can be attributed to study designs and small cohort sizes. Moreover, only a limited number of published studies were available in this meta-analysis and no RCTs were included; the nature of nonrandomized trials may confound variables. Additionally, some studies have relatively small sample sizes (fewer than 20 patients) and thus may overvalue the efficacy of the switching therapy.

Conclusions

In short, our results presented positive evidence for conversion to aflibercept treatment in patients with DME resistance to either bevacizumab or ranibizumab. Even if this alternative strategy showed advantages in visual acuity and retina morphological changes at 1 month and 3 months follow-up time, more long-term data is needed to improve the accuracy of this meta-analysis, and provide guidance to clinicians.

Acknowledgments

The authors sincerely appreciate the efforts from Nathan E. Reticker-Flynn (postdoctoral scholar, Stanford University) for the English editing and revising of our study.
Funding: None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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Cite this article as: Liu Y, Cheng J, Gao Y, Qin L, Min X, Zhang M. Efficacy of switching therapy to aflibercept for patients with persistent diabetic macular edema: a systematic review and meta-analysis. Ann Transl Med 2020;8(6):382. doi: 10.21037/atm.2020.02.04

Supplementary

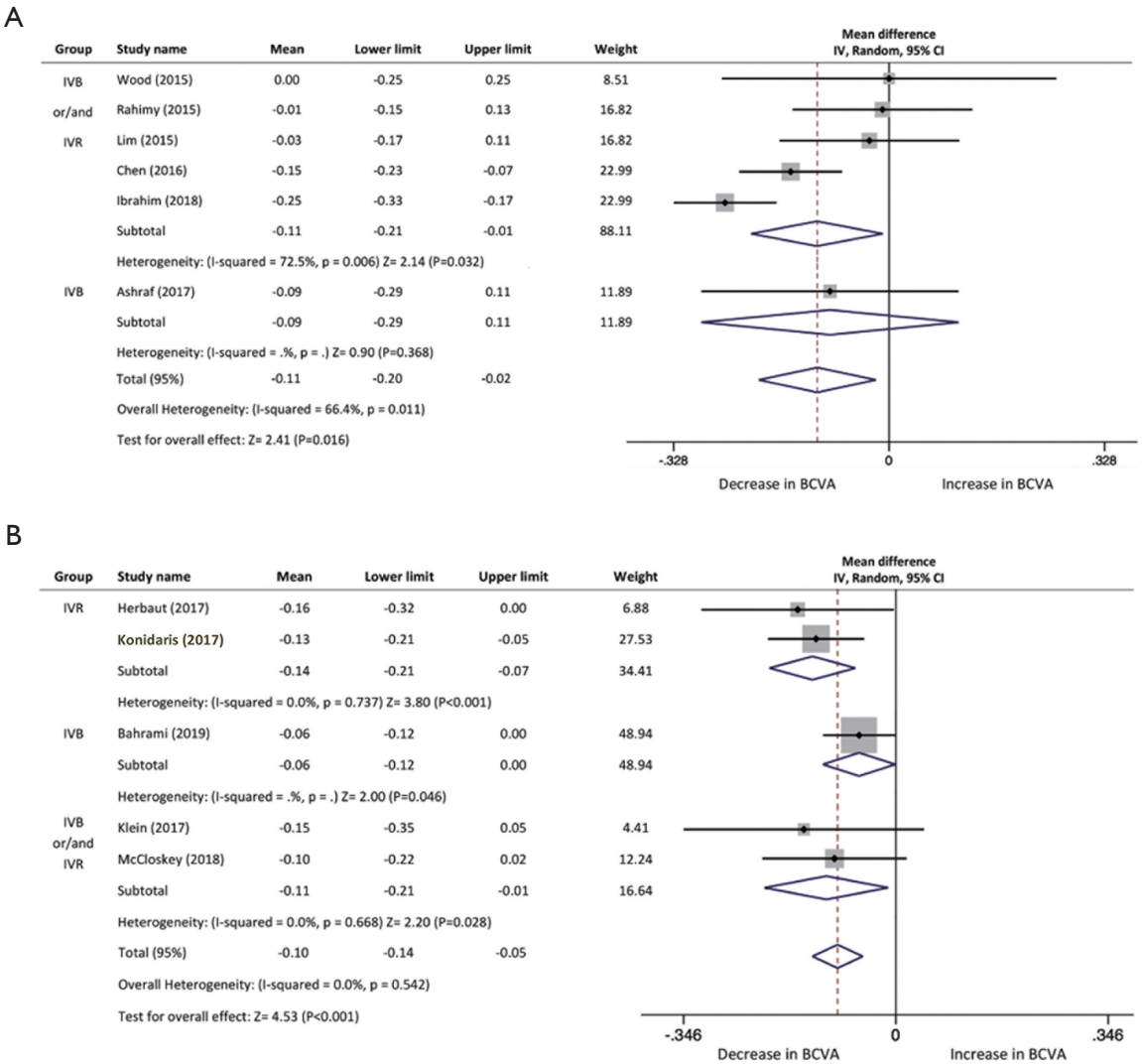

Figure S1 Forest plot showing outcomes of best-corrected visual acuity (BCVA, logMAR) in different subgroups (IVB, IVR, IVB and/or IVR) after the switch. (A) 1 month; (B) 6 months.

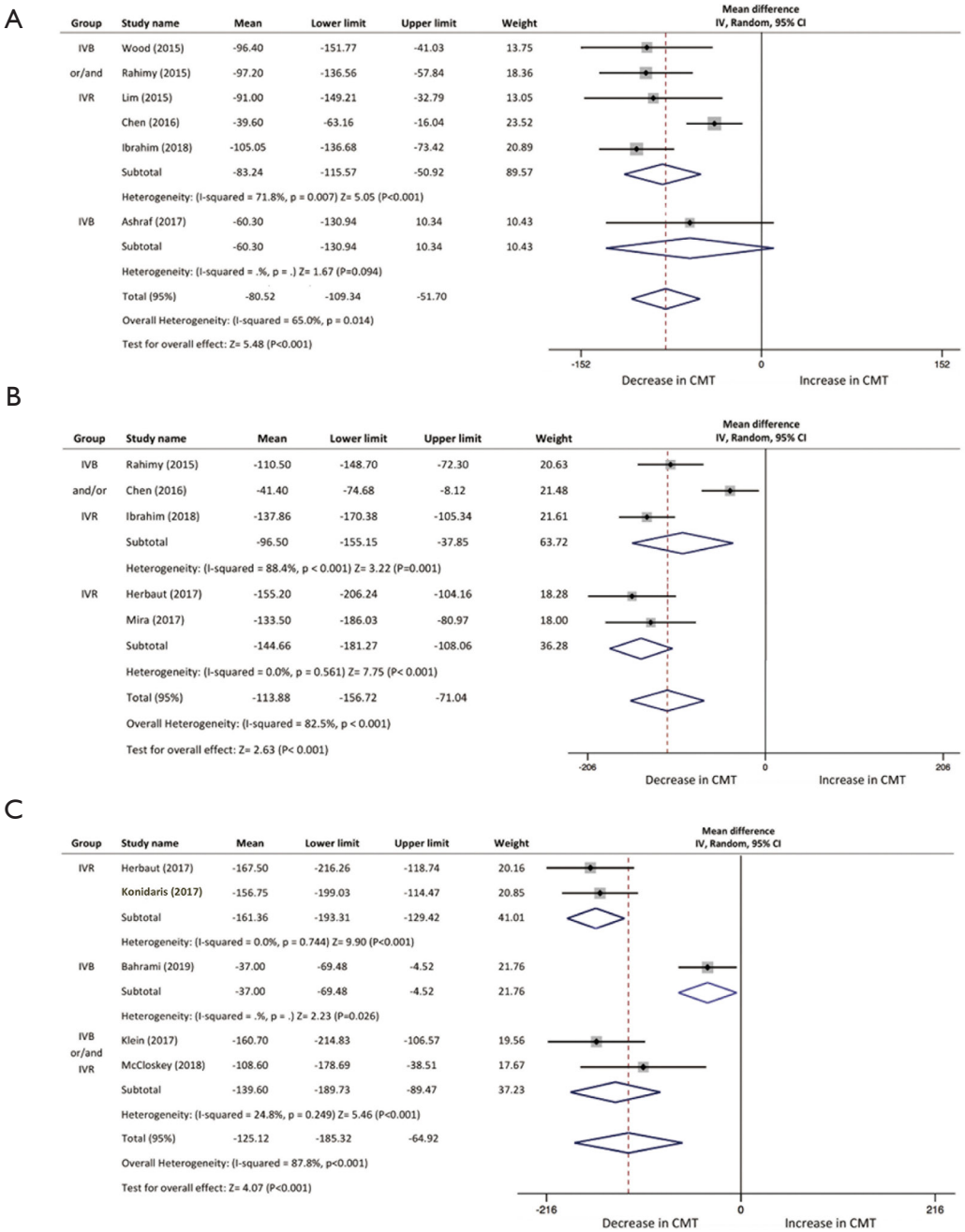

Figure S2 Forest plot showing outcomes of central macular thickness (CMT, μm) in different subgroups (IVB, IVR, IVB and/or IVR) after the switch. (A) 1 month; (B) 3 months; (C) 6 months.

Table S1 Study characteristics of the fourteen trials in the meta-analysis

Authors	Year	Adverse	Definition of treatment resistance	Inclusion/exclusion criteria
Herbaut *et al.*	2017	No serious adverse event following intravitreal injections	Persistent DME defined by a loss of the foveal pit, and a CRT >300 µm on SD-OCT responsible for a loss of vision [pre-switch visual acuity (VA)]	Inclusion: Patients with type 1 or 2 diabetes, with persistent DME. Only patients who received at least the first 3 monthly aflibercept injections were included in the study. Exclusion: other ocular conditions impairing vision or complication of diabetic retinopathy, fewer than three IVR prior to the switch to aflibercept, and incomplete imaging or clinical data
Bahrami *et al.*	2019	Notable ocular adverse events included a rhegmatogenous retinal detachment. There was no progression of cataract severity or raised IOP in any of the study eyes, and no patients required medical or surgical intervention for cataract or raised IOP	Persistent central macular thickening identified by OCT and/or a loss of 10 ETDRS letters in vision despite 4-weekly intravitreal injections	Inclusion: Patients aged 18 or older, with DME secondary to type 1 or type 2 diabetes mellitus, BCVA between 34 and 85 ETDRS letters, retinal thickness greater than 300 µm in the central 1 mm ETDRS field on SD-OCT and at least 4 previous IVB (2.5 mg/0.1 mL) in the 6 months prior to baseline examination. Exclusion: Intravitreal steroid therapy or vitrectomy surgery in the study eye within 3 months of baseline, cataract surgery or macular laser within 2 months of baseline, pregnancy, and uncontrolled diabetes mellitus (HbA1c >12%)
McCloskey *et al.*	2018	No significant systemic or ocular adverse events during our study period	No decline, partial resolution or increase in fluid on OCT comparable with fundal examination and declining or no improvement in VA	Inclusion: DMO Patients received at least three previous consecutive IVR (0.5 mg), IVB (1.25 mg) or both in the 6 months prior to conversion. Exclusion: Patients received procedures affecting possible visual outcomes including phacoemulsification, YAG capsulotomy and corticosteroid treatment during the treatment period
Nixon *et al.*	2018	No ocular or non-ocular adverse events were reported in the patient population during the study	Persistent fluid on SD-OCT following at least 3 consecutive IVR	Inclusion: Aged 18 or older; ability to complete study; more than 3 IVR over previous 6 months; persistent fluid on OCT, VA 6/30. Exclusion: Intraocular pressure 25 mmHg; prior retinal surgery or significant subretinal scarring, cataracts, or vitreous hemorrhage; anti-VEGF treatment within prior 30 days; intravitreal steroid treatment within prior 6 months; MI, TIA, or CVA within prior 90 days; current pregnancy or lactation.
Wood *et al.*	2015	Treatment was well-tolerated with no adverse events	Persistent intraretinal or subretinal fluid despite at least three monthly IVR or IVB	Inclusion: DME patients with persistent retinal fluid despite regular (every 4 to 6 weeks) IVR 0.3 mg and/or IVB 1.25 mg who were switched to aflibercept 2 mg. Exclusion: Patients with other vision-limiting conditions besides DME or other possible causes of macular edema.
Rahimy *et al.*	2016	No ocular adverse events; no systemic thromboembolic adverse events	Persistent DME with no reduction, incomplete resolution, or an increase in central subfield thickening by SD-OCT, necessitating additional anti-VEGF therapy at the time of conversion	Inclusion: Patients aged 18 years or older with diabetes mellitus (type 1 or type 2), macular edema and commensurate center-involving DME (CMT >300 µm) by SD-OCT imaging; persistent exudative fluid; eyes treated with at least 4 consecutive IVR/IVB performed at the exact same interval prior to conversion and with at least 2 IVA afterward at that same interval. Exclusion: Any of the following treatments during the 6-month period prior to anti-VEGF conversion or after: intravitreal or sub-Tenon injections of corticosteroids, *et al.*; concomitant ocular diseases aside from NDPR in the treated eye: AMD, CRVO/BRVO, choroidal neovascularization, history of ocular trauma, or prior intraocular surgery
Konidaris *et al.*	2017	N/A	N/A	N/A
Mira *et al.*	2017	No ocular or systemic thromboembolic adverse events were registered	Persistent or increasing sub- or intraretinal fluid on SD-OCT after 3 or more consecutive monthly injections regardless of vision	Inclusion: Diabetic type 2 patients aged 18 years or older with DME unresponsive to anti-VEGF with a minimum of 3 injections 4 months before switch and 3 months of follow-up. Exclusion: Macular edema secondary to a cause other than diabetes, complications of diabetic retinopathy, myopia greater than –6 diopters, ocular surgery 6 months prior to switch, presence of drüsens, and incomplete clinical data
Klein *et al.*	2017	No ocular adverse events. No systemic adverse events such as thromboembolic phenomena.	Persistent cystic change with ≤15% decrease in CRT over the 6 months prior to IAI switch despite having at least 4 total treatments for DME, with at least 3 of these treatments being intravitreal anti-VEGF injections (excluding IAI)	Inclusion: Recalcitrant to current therapy; age 18 years or older; clear ocular media; baseline IOP of 21 mmHg or less with or without pressure-lowering drops in patients previously treated with corticosteroids; Snellen VA between 20/40 and 20/300. Exclusion: Previous IAI in the study eye and history of systemic anti-VEGF use
Lim *et al.*	2015	N/A	N/A	Inclusion: Refractory DME treated with IVR and/or IVB. Exclusion: Other visually significant ocular pathology and complications of diabetic retinopathy, loss to follow-up, fewer than three IVR and/or IVB prior to conversion to aflibercept, and incomplete imaging or clinical data
Ashraf *et al.*	2017	N/A	N/A	Inclusion: Patients with diabetes mellitus (type 1 or 2) aged over 18 with center-involved DME, nonresponse to bevacizumab and treatment duration of less than 9 months since the start of therapy. Exclusion: Vitreoretinal interface abnormality on SD-OCT that may contribute to macular edema or presence of any other significant macular pathology or postsurgical macular edema, as well as previous treatment duration of greater than 9 months prior to switching
Laiginhas *et al.*	2018	N/A	N/A	Inclusion: DME refractory to bevacizumab, aged over 18 with a history of diabetes mellitus (type 1 or 2), baseline evidence of clinically significant macular edema and commensurate center-involving DME (CMT >300 µm) SD-OCT imaging. Exclusion: Intravitreal treatment within the 6 months before the switch, the presence of other retinal pathologies causing macular edema, recent ocular surgery (within 6 months), concomitant ocular morbidity that significantly affected the visual acuity, presence of epiretinal membranes/ vitreomacular traction and incomplete medical records
Ibrahim *et al.*	2019	Only four cases of subconjunctival hemorrhage were reported, with no other serious ocular and systemic adverse events	N/A	Inclusion: Resistant DME defined as above. Exclusion: Unwillingness to participate; significant cataract or corneal opacity; DME associated with PDR; history of laser treatment or steroid injection in the previous 6 months, co-existing retinal pathology; history of cataract surgery in the previous 12 months, associated optic nerve disorders, glycosylated hemoglobin higher than 8% at the time of participation, ischemic heart disease, or previously complicated intravitreal injection of anti-VEGF; fewer than 3 consecutive IVI
Chen *et al.*	2017	No systemic adverse events, such as thromboembolic events, were noted	A paradoxical increase in CFT and gain in BCVA of less than 1 line at 1 month after at least 3 months of continuous treatment compared with before bevacizumab or ranibizumab administration	Inclusion: Aged over 18 with history of diabetes mellitus and clinically significant macular edema defined by the ETDRS and center-involving DME; DME resistance to bevacizumab or ranibizumab. Exclusion: Patients with prior ocular trauma, vitreomacular adhesion or traction, epimacular membrane, tractional retinal detachment, vitreous hemorrhage, other ocular disorders, prior intravitreal or sub-Tenon injections of corticosteroids or intravitreal corticosteroid implants, or other previous intraocular surgeries

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CFT, central foveal thickness; CMT, central macular thickness; CRT, central retinal thickness; CRVO, central retinal vein occlusion; DME, diabetic macular edema; DMO, diabetic macular oedema; ETDRS, Early Treatment of Diabetic Retinopathy Study; IOP, intraocular pressure; IVA, intravitreal aflibercept; IVB, intravitreal bevacizumab; IVI, intravitreal aflibercept injection; IVR, intravitreal ranibizumab; N/A, not available; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; SD-OCT, spectral-domain optical coherence tomography; VA, visual acuity; VEGF, vascular endothelial growth factor.