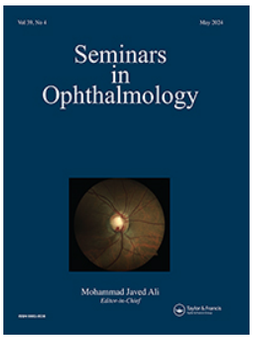

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REVIEW

Safety and Efficacy of Brolucizumab in the Treatment of Diabetic Macular Edema and Diabetic Retinopathy: A Systematic Review and Meta-Analysis

Hashem Abu Serhan[a], Mohammad J. J. Taha[b], Mohammad T. Abuawwad[b], Abdelaziz Abdelaal[c,d], Sara Irshaidat[e], Leen Abu Serhan[f], Qusai Faisal Abu Salim[g], Nour Awamleh[h], Basel Abdelazeem[i], and Ayman G Elnahry[j,k]

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ABSTRACT

Purpose: To investigate the efficacy and safety of brolucizumab in diabetic macular edema (DME) and diabetic retinopathy (DR).

Methods: In this systematic review and meta-analysis, an electronic search was done to acquire all articles describing brolucizumab use in patients with DME and DR. The review was prospectively registered on PROSPERO (CRD42022382625). Collected articles were filtered through two stages by independent reviewers. Data were extracted from the included articles and then analyzed accordingly.

Results: Brolucizumab induced significant improvement in best-corrected visual acuity and was either better or non-inferior to other types of anti-VEGF (MD −0.64 mu, 95% CI [−1.15, −0.13], $P = .01$); the same observation was noted with regards to central subfield macular thickness (CSMT) (MD −138.6 mu, 95% CI [−151.9, −125.3], $P = .00001$). Brolucizumab was reported to be relatively safe for use in diabetic patients, with few adverse events observed, with a higher frequency of adverse events in relation to the 3 mg dose compared to the 6 mg dose.

Conclusion: Brolucizumab is a new drug that has potential advantages in efficacy over other anti-VEGF agents in the treatment of DME and DR. It showed significant improvement in BCVA and CSMT with the possibility of a lower dosing schedule compared to other agents. Although observed in low frequency, sight-threatening adverse effects appear to occur more frequently compared to other anti-VEGF agents. The main observed adverse event was retinal vasculitis which was seen more commonly with the 3 mg dose versus the 6 mg dose.

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Anti-VEGF; BOVU; brolucizumab; macular edema; vascular endothelial growth factor

INTRODUCTION

Diabetes mellitus (DM) is becoming more prevalent worldwide, with an estimated 440 million people suffering from the disease by 2030.[1] According to previous reports, DM is the primary cause of blindness in the U.S. between the ages of 20 and 74.[2] Diabetic retinopathy (DR) affects about 29% of diabetic individuals, while diabetic macular edema (DME) affects about 3%.[3] With the increasing prevalence of DM, a corresponding concern for DR complications is also growing. The global incidence of DR is predicted to increase from 126.6 million cases in 2010 to 191 million cases annually by 2030.[4,5] DME is a major cause of vision loss among work-age individuals.[6] It can develop at any stage or severity of DR and can significantly impact vision, making it a serious complication of DM. The primary objective of treating DME is to enhance patients' visual function and quality of life.[7] The gold standard for treating retinal vascular disorders, such as DME, is intravitreally injected anti-vascular endothelial growth factor (VEGF) agents.[8,9] They are recommended as the first-line treatment by various clinical guidelines.[10] The US Food and Drug Administration (FDA) has approved multiple anti-VEGF molecules for intraocular use, with differing efficacy in the treatment of DME.[11,12] A significant proportion of patients with DME, about 15–20% of cases, however, do not adequately respond to anti-VEGF medication which creates the need for further drug and treatment protocol development.[13]

As evidenced by persistent macular edema despite 24 months of anti-VEGF medication, up to 56.7% of DME eyes treated with bevacizumab and 40% of those treated with ranibizumab are reported as non-responders.[14] Switching to a different medication, such as corticosteroids or an alternative anti-VEGF drug, is a viable option in cases of poor response,[15,16] and several studies have shown benefit when switching from one anti-VEGF agent to another.[17,18] Furthermore, in the protocol of the Diabetic Retinopathy Clinical Research Network (DRCR.net), aflibercept was superior to both bevacizumab but not ranibizumab in patients with vision worse than 20/50. It is essential to also

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emphasize the importance of treatment of persistent DME, as the MYRROR study has demonstrated that a delay in treatment can have an impact on visual outcomes possibly due to structural changes in the retina from chronic edema.[19]

Brolucizumab, a monoclonal antibody that binds to VEGF-A, was approved in 2019 by the FDA and has a unique single-chain antibody fragment and low molecular weight, providing durability and potential advantages over other anti-VEGF agents.[20,21] Brolucizumab is administered as an intraocular injection, with a recommended dosage of 6 mg every 4 weeks for the first 3 months, followed by every 8–12 weeks. Brolucizumab was reported non-inferior to aflibercept in phase 3 clinical trials of HAWK and HARRIER, with superior anatomical outcomes obtained with quarterly (q12-week) doses in the treatment of nAMD.[22] In 200 sites in 36 countries, two more 3 phase clinical trials, KESTREL and KITE, are now being conducted to determine whether brolucizumab is non-inferior to Aflibercept in terms of functional and morphological improvement for the treatment of DME over a 52-week period.[23] The preliminary findings from these trials have revealed encouraging visual acuity and anatomical results following one year.[23] Brolucizumab has, however, been linked to instances of retinal vasculitis and retinal vascular occlusion, usually in the presence of other indications of intraocular inflammation (IOI) as suggested by several recent case series and case reports.[24] This has created some concern regarding its intraocular use.

Several reviews have been performed to evaluate the use of brolucizumab for the treatment of AMD. This is the first systematic review and meta-analysis to evaluate the up-to-date data on the safety and efficacy of brolucizumab in the treatment of DME and DR.

MATERIALS AND METHODS

Study Protocol and Database Search

This research was carried out in accordance with the Preferred Reporting for Systematic Review and Meta-Analysis (PRISMA) recommendations.[25,26] The study adhered to the tenets of the Declaration of Helsinki and the necessity for institutional review board (IRB) approval was not required since it did not involve human subjects. In December 2022, our protocol was registered on PROSPERO [registration number: CRD42022382625]. Meanwhile, on December 25–26, 2022, we searched six electronic databases [PubMed, Scopus, EMBASE, Web of Science, CENTRAL, and Google Scholar] to retrieve all studies that reported the use of brolucizumab in diabetic macular edema and/or diabetic retinopathy using the following keywords: ((Brolucizumab or BOVU) AND (macular edema OR diabetic retinopathy)). Medical Subject Headings (MeSH) terms were also added whenever applicable to retrieve all relevant studies based on their indexed terms in included databases. Of note, only the first 200 records from Google Scholar were retrieved and screened as per the recent recommendations.[25] Noteworthy, an updated database search was carried out on March 15th, 2023 to include any newly published studies before the official synthesis of collected data.

Additionally, on February 1st, 2023, after finishing the screening process, we conducted a manual search of references to identify any relevant studies that we could not identify through the original database search. This search was conducted through: (1) searching similar articles of the finally included articles in our review through the "similar articles" option on PubMed, (2) searching the reference list of finally included articles in our review, and (3) searching through Google with the keywords used in the original database search.

Eligibility Criteria

We included original research papers that discussed the use of brolucizumab in DME and/or DR. We included all of the following study designs: randomized controlled clinical trials (RCT), retrospective studies, case series and case reports. Studies were included regardless of the language of publication. Meanwhile, studies were excluded if they were (1) non-original research (i.e., reviews, commentaries, guidelines, editorials, correspondence, letters to editors, etc.), (2) unavailable full-texts, (3) duplicated records or records with overlapping datasets, (4) studies reporting using brolucizumab for indications other than DME or DR, where outcomes for DME or DR were not reported separately (5) studies not involving brolucizumab.

Screening and Study Selection

Retrieved records from the database search were exported into EndNote software for duplicate removal before the beginning of the screening phase. Records were then imported into an Excel (Microsoft, USA) Sheet for screening. The screening was divided into two steps: title and abstract screening and full-text screening. The full texts of eligible articles were then retrieved for screening before being finally included in the review. Both steps were carried out by three reviewers [SI, LAS, QAS]. Any differences between reviewers were solved through group discussions, and the senior authors [HAS, AGE] were consulted if reviewers could not reach an agreement.

DATA EXTRACTION AND ASSESSMENT OF METHODOLOGICAL QUALITY AND RISK OF BIAS

The data extraction was performed by three reviewers [SI, LAS, QAS] through a data extraction sheet that was formatted through Excel (Microsoft, USA). This sheet consisted of six parts. The first part included the baseline characteristics of included studies [title, authors' names, year of publication, country, and study design] and patients as well [sample size, age, and gender]. The second part included data on brolucizumab (number of injections, laterality, optical coherence tomography (OCT) findings post-injection, baseline and post-treatment best corrected visual acuity (BCVA), baseline and post-treatment Diabetic Retinopathy Severity Scale (DRSS) score, the indication for treatment, and whether the patient was treatment-naive or not). The third part summarized the medical history of reported cases (i.e., systemic diseases, cardiovascular diseases, cerebrovascular diseases, immunological diseases, history of eye trauma, previous eye diseases, and previous ocular surgeries). The fourth part included a thorough assessment of adverse events following the injections including intraocular inflammation, systemic

adverse events, the rate of progression to PDR, and the rate of persistent DME. The fifth part included the assessment of fluorescein angiography and OCT angiography findings if available. The sixth part included the quality assessment of included studies. Methodological quality and risk of bias were assessed using the NIH Quality Assessment Tool for the specific study type.[27] (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).

Data Synthesis

Acquired data was tabulated and reorganized, then qualitative and quantitative analysis were performed. Qualitative analysis was done through table columns comparison using the Statistical Package for Social Sciences (SPSS) version 27 (IBM SPSS Corp, SPSS Statistics ver. 26, USA). Descriptive analysis was used to display categorical variables as percentages and frequencies while presenting numerical variables as a mean and standard deviation to evaluate the data quantitatively. The significance of the data was determined using a categorical Chi-square test. All statistical tests were conducted with a 95% confidence interval and a 5% error margin. A p-value of less than 0.05 was considered statistically significant. Quantitative analysis was performed on categorical basis through meta-analysis executed using Cochrane's RevMan software. In RCTs, visual acuity (VA) was frequently quantified and reported as an Early Treatment Diabetic Retinopathy Study (ETDRS) letter score. When the logarithm of the minimum angle of resolution (logMAR) or Snellen chart scores were used to measure VA, the score was converted to approximate ETDRS letter scores using the method proposed by Gregori et al.,[28] which was used in quantitative analysis.

$$\text{logMAR} = -1 \times \log(\text{Snellen fraction})$$

$$\text{Approximate ETDRS letter scores} = 85 + 50 \times \log(\text{Snellen fraction})$$

RESULTS

Study Selection

Our search yielded 487 articles. 453 were excluded at the title and abstract level, leaving 34 articles for full-text review. Eight articles with a total of 926 patients satisfied the inclusion criteria and were included in the qualitative and quantitative analyses. Figure 1 shows PRISMA chart for the selection of included articles.

Study Characteristics

Included studies were 4 interventional studies and 4 observational studies. Duration of study ranged from 2 to 52 weeks. Patients were mainly in the older age group and males were of higher frequency than females (81.425%). Included studies were good to high in quality. A brief summary of the characteristics of included studies is available in Table 1. Two

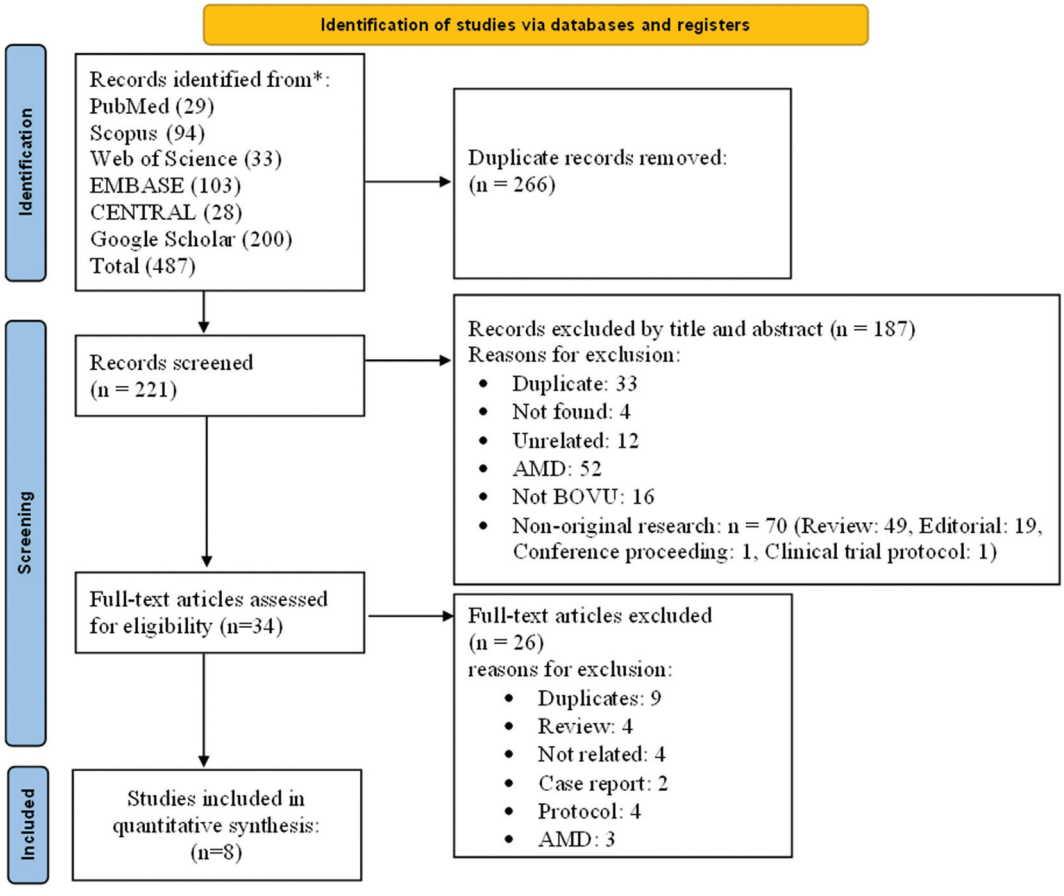

Figure 1. Shows PRISMA chart for selection of included articles.

Table 1. Summary of studies included in this review.

ID	Year	Country	Study design	Duration	Sample size	Age	Sex	Race	Quality
Brown et al.[23]	2022	USA	2 Randomized Controlled Clinical Trials	52 weeks	KESTREL (566)	<65	M: 355/F: 211	White (462), Black or African American (24), Asian (77), Japanese (62), Indian (10), Chinese (3), American Indian/Alaska Native (2), Native Hawaiian/Other Pacific Islander (2)	10
					KITE (360)	≥65	M: 235/F: 125	White (265), Black or African American (4), Asian (91), Indian (25), Chinese (30), Korean (19), Vietnamese (1)	
Busch et al.[29]	2022	Germany	Cross-Sectional study	-	192 serum and 54 vitreous samples	-	M: 100/F: 92	-	10
Chakraborty et al.[30]	2022	UK	Retrospective, consecutive, interventional, uncontrolled, single-center study	24.6 ± 4.05 weeks	13	52.9 ± 4.6 years	M: 7/F: 6	-	9
Murray et al.[31]	2021	USA	Retrospective	3 months	98	34–95	M: 52/F: 46	Caucasian (51), Hispanic (42), African American (3), and Asian (2).	10
Chakraborty et al.[32]	2022	India	Case Report	4 weeks	1	48	M	Indian	7
Mahapatra et al.[33]		India	Case Series	6 months	3	case 1:54y/case 2:49/case 3:55	M/F/M	Indian	8
Hirano et al.[34]	2023	Japan	Case Report	unknown	1	68	F	Japanese	11
Chakraborty et al.[35]	2021	India	Case Series	16 weeks	3 eyes	Case 1: 56y Case 2: 37y case 3: 49 y	1: F 2: M 3: M	Indian	7

studies utilized brolucizumab 3 mg, three trials used brolucizumab 6 mg, and one research compared both doses, the remaining studies did not mention a specific dose. All studies looked at how brolucizumab affected BCVA and central subfield macular thickness (CSMT) except for one study that solely looked into the existence of antibodies to brolucizumab in both the serum and vitreous fluid, with no consideration for dosages, CSMT, or BCVA. The effect of brolucizumab was evaluated in one study on the contralateral eye, and the results were significant in both the injected and contralateral eye,[32] as shown in Tables 2 and 3. The main study was the KESTREL and KITE study,[36] which reported two major clinical trials that used brolucizumab in the treatment of DME [Tables 2 and 3]. The statistical meta-analysis was limited to BCVA and CSMT measurements because they're the only variables reported in all included studies.[23]

BCVA

All studies showed significant improvement in the BCVA from the baseline to different endpoint measurements. In addition, brolucizumab was reported to be non-inferior to other anti-VEGF drugs (aflibercept).[23]

The overall mean difference of the effect of brolucizumab on BCVA from the baseline to different endpoints showed the following results (Mean Difference −0.64 on LogMAR, 95% CI [−1.15, −0.13], $P = .01$); and the pooled studies were heterogonous (Heterogeneity: $Chi^2 = 2540.1$, ($p = .00001$)) (Figure 2).

Central Subfield Macular Thickness (CSMT)

The overall mean difference of the effect of brolucizumab on CSMT from the baseline to different endpoints yielded the following: (Mean Difference −138.6 micrometer, 95% CI [−151.9, −125.3], $P = .00001$); and the pooled studies were heterogenous (Heterogeneity: $Chi^2 = 2529.24$, ($p < .01$)) (Figure 3).

Other Significant Effects

Subretinal Fluid And/Or Intraretinal Fluid

According to Brown et al., at week 52, a lower proportion of subjects in the brolucizumab arms had intraretinal (IRF) and/or subretinal (SRF) compared with aflibercept in both KESTREL and KITE with a treatment difference of − 14.1% (95% CI: −23.3, −4.6), and − 13.2% (95% CI: −23.2, −3.8) between brolucizumab 3 mg and 6 mg, respectively, and aflibercept.[23]

Diabetic Retinopathy Status

Brown et al. reported on the improvement in the DRSS score following treatment. They found that the proportion of subjects with an improvement greater than 2-steps was higher in the brolucizumab 3 mg arm (28.6%) and 6 mg arm (29.6%) compared with the aflibercept arm (21.7%) in KESTREL. On the other hand, the proportions were comparable in the KITE study (brolucizumab 6 mg, 29.0%; aflibercept, 27.7%).[23]

Safety

Brolucizumab was linked to 6 incidences of retinal vasculitis in DME patients. However, with the exception of one patient who had severe visual loss (the author indicates that this patient has been diagnosed with past head trauma, which could explain the poor prognosis[23]), the majority of patients have had a favorable prognosis and complete resolution. Ocular adverse effects were more likely in patients who received brolucizumab 3 mg rather than 6 mg. In these

Table 2. Overview of BCVA changes after Brolucizumab across included studies.

TITLE	No. of patients	Baseline BCVA (ETDRS)	Mean Change in BCVA ± std	Post-treatment BCVA
Brown et al. (KESTREL)[23]	190	3 mg: 65.7 (11.09)	9.2 ± 0.57	
	189	6mg: 66.6 (9.67)	7.3 ± 0.66	
Brown et al. (KITE)[23]	179	66.0 (10.77)	10.6 ± 0.62	
Chakraborty et al.[32]	13	58.74	78.48	65.10 4w
	13		78.48	65.54 8w
	13		78.48	65.54 12w
	13		82.93	61.14 16w
Chakraborty et al.[32] Second dose	9	59.07	82.93	60.08 28w
Murray et al.[31]	98	40.53	76.19	50.05
Chakraborty et al.[30]	1	61.14 OD		OU: 69.94
		46.09 OS		
Mahapatra et al.[33]	3	Case1: 45.03		Case1: 75.48
		Case2: 10.01		Case2: 25.06
		Case3: 10.01		Case3: +20.00
Hirano et al.[34]	1	74.79 OD		After two doses: 77.69 OD
				One month after 3rd dose: 74.79
Chakraborty et al.[35]	3	Case1: 61.14		80.15
		Case2: 69.94		80.15
		Case3: 69.94		80.15

Table 3. Summary of CST results in included studies.

TITLE	No. of patients	CSMT at baseline	CSMT post Tx	Mean CSMT ± std
Brown et al. (KESTREL)[23]	190	3mg: 456 ± 118	N/A	−167.1 ± 6.54
	189	6mg: 453 ± 123	N/A	−171.9 ± 6.18
Brown et al. (KITE)[23]	179	481 ± 132	N/A	−197 ± 6.3
Chakraborty et al.[32]	13	402 ± 60.1	273.33 ± 25.8 4w	−128.67 ± 65.4
	13		263.55 ± 22.01 8w	−138.45 ± 64
	13	419 ± 60.3	295.11 ± 13.38 12w	−106.89 ± 61.57
	13		378.3 ± 29.8 16w	−40.7 ± 67.26
Chakraborty et al.[32] Second Dose	9	402 ± 60.1	295.1 ± 13.3	−106.9 ± 61.55
Murray et al.[31]	98	412.2 ± 77.83	340.7 ± 68.99	−71.5 ± 104.98
Chakraborty et al.[30]	1	321µm in OD	272µm in the OD	
		637µm in OS	248µm in the OS	
Mahapatra et al.[33]	3	Case1: 434	Case1: 180	
		Case2: 298	Case2: 150	
		Case3: 402	Case3: 167	
Hirano et al.[34]	1	368µm	253µm	
Chakraborty et al.[35]	3	Case 1: 621µm	Significant reduction at week 12 that recurrence at week 16	
		Case 2: 645µm	Complete reduction at week 12 that recurrence at week 16	
		Case 3: N/A	Complete resolve at week 12 that recur at week 16	

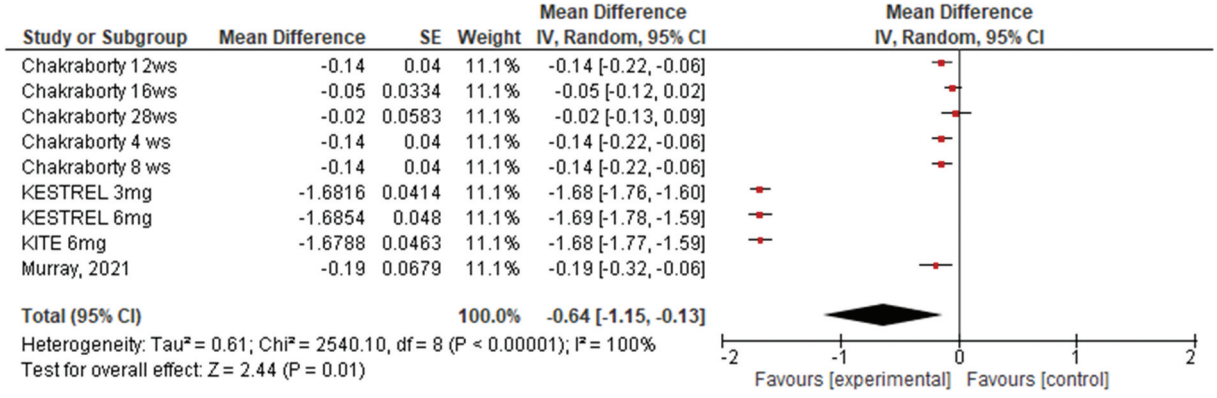

Figure 2. Shows the meta-analysis of effect of Brolucizumab on BCVA across included articles.

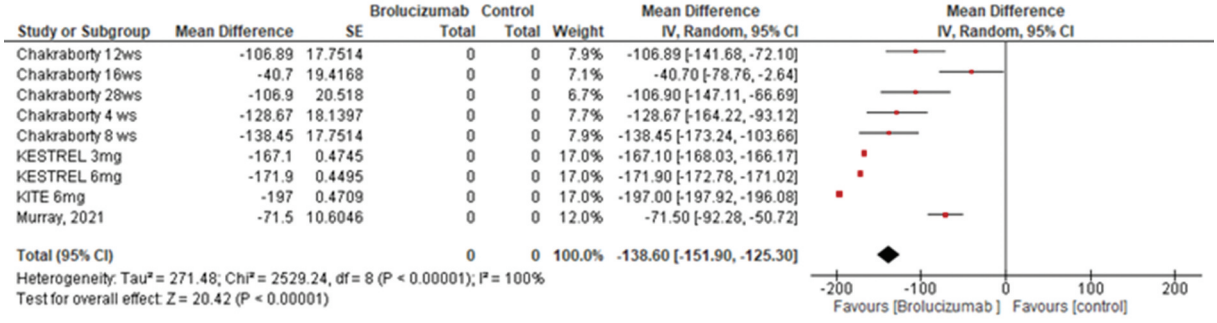

Figure 3. Shows the meta-analysis of effect of Brolucizumab on CSMT across included articles.

patients, many more eye problems have been described. According to Busch et al.,[29] in a study on 192 blood samples and 59 vitreous bodies to investigate the role of immunity in the incidence of ocular problems after brolucizumab in comparison to other Anti-VEGF alternatives, the following results were obtained: (1) Higher antibody concentrations were associated with female gender and diabetic retinopathy; (2) Anti-drug antibodies (ADAs) can develop in both patients with or without prior brolucizumab exposure. (3) Furthermore, ADAs were less common in vitreous samples compared to serum samples (13% vs. 20.4%) expect for DR patients (Table 4).

Table 4. Safety of brolucizumab as observed by included studies.

TITLE	Dose	Type and number of events	Onset time (days)	Prognosis	Percentage of Ocular SAE
Brown et al. (KESTREL)[23]	3mg	Three cases of retinal vasculitis One case of Retinal vein thrombosis	(115, 96, 203) 291 days	- Mild to moderate - Resolved with routine clinical care without sequelae	3.7% of subjects in the brolucizumab 3 mg arm 1.1% of subjects in the brolucizumab 6 mg arm 2.1% of subjects in the aflibercept arm
	6mg	Two cases of retinal vasculitis progressing to RAO	114 days 136 days		
Brown et al. (KITE)[23]	6mg	One case of RAO	N/A	Vision loss: −75 letters decline in visual acuity,	
Busch et al.[29]	N/A	- Two patients with severe vision loss due to occlusive retinal vasculitis - One patient moderate IOI and signs of segmented blood flow	N/A	Full recovery on corticosteroids in the patient with IOI	In the vast majority of vitreous samples, brolucizumab ADA levels were obtained from patients who had never received brolucizumab.
Chakraborty et al.[32]		There was no evidence of inflammation, vasculitis, or any other ocular or systemic adverse effects in any of the eyes.			
Murray et al.[31]		There was no evidence of inflammation, vasculitis, or any other ocular or systemic adverse effects in any of the eyes.			
Chakraborty et al.[30]		There were no ocular or systemic adverse events after brolucizumab therapy.			
Mahapatra et al.[33]		There were no ocular or systemic adverse events after brolucizumab therapy.			
Hirano et al.[34]	3mg	OD retinal arterial occlusive vasculitis (Bilateral Injection)	1 month	Decline from 20/28 to 20/32, and after one year, BCVA reached 20/50	It is essential to detect IOI and subsequent retinal artery occlusive vasculitis at an early stage. Oral prednisolone is used to treat severe brolucizumab-associated IOI in patients with nAMD. However, due of the possibility of elevated blood glucose levels, oral prednisolone should be used with caution in patients with DME.

Abbreviations; ADA: Anti-Drug Antibodies, BCVA: Best Corrected Visual Acuity, DME: Diabetic Macular Edema, IOI: Intra-Ocular Inflammation, RAO: Retinal Artery Occlusion, SAE: Serious Adverse Events (Any adverse event that causes a >30 decrease in BCVA and lasts more than one hour),[37] nAMD: Neovascular Age-Related Macular Degeneration.

DISCUSSION

By merging the data from 8 studies that included a total of 926 diabetic patients, this systematic review and meta-analysis attempted to provide an up-to-date investigation of the safety and efficacy of brolucizumab in the treatment of DME and DR. Our findings demonstrated that the use of brolucizumab had considerable positive effects on BCVA, CSMT, IRF, SRF, and the status of DR. Furthermore, four included studies mentioned ocular side effects that emerged after using brolucizumab.

The main outcome of this study was that brolucizumab has a beneficial role in reducing macular thickness in DME patients. The mean reduction in CSFT was 138.6 micron, CI [−151.9, −125.3], from the CSFT baseline. The best improvement was associated with using brolucizumab at a dose of 6 mg in KITE study (−197 micron reduction in CSFT) at week 52 of follow up, after receiving a median of 7 intravitreal injections. These results were similar to the findings of the Dugel et al. study. In the Dugel et al. study, significant CSFT reductions from baseline were observed at Week 48 with brolucizumab 6 mg. The reduction was reported as (−172.8 micron) in HAWK and (−193.8 micron) in HARRIER studies (i.e., Dugel et al. study).[22] On the contrary, results of the Hänsli et al. study were less encouraging, as they reported a reduction of only −74 microns (baseline 394.2, 12 months follow-up 320.0).[36] This can be attributed to the difference in population; in our cohort, both naïve and previously treated eyes were investigated, while the Hänsli et al. paper only included patients who switched to brolucizumab after either complaining of persistent disease activity with intra- and/or subretinal fluid and/or receiving a high treatment demand with other anti-VEGF agents.

In terms of BCVA, the total improvement from baseline through various measurement points is 53.07 in the ETDRS score. The best reduction was associated with a similar dose and follow-up of the CSMT (KITE study, dose of 6 mg, week 52 of follow-up, median of 7 IVT), which is much higher than the results of the previous systematic review conducted by Hänsli C et al.,[36] which showed a change of only 69.41 to 75.48 ETDRS. An observation that could be explained by the same reasons for differences in CST outcome.[38] However, the results of the main studies on the effect of brolucizumab on nAMD were similar in the least squares [LS] mean: +6.6 [6 mg] and + 6.1 [3 mg] letters with brolucizumab in HAWK; +6.9 brolucizumab 6 mg in HARRIER in comparison to + 7.3 [6 mg] and + 9.2 [3 mg] letters with Brolucizumab in KESTREL; and + 10.6 brolucizumab. These numbers indicate that brolucizumab offers similar improvement indices as compared to other intravitreal injections for similar cases of DME. In a meta-analysis on the effects of ranibizumab in BCVA improvement, the mean effect was + 7.01 (2.56–11.39) which is comparable to our findings.[39] Intravitreal aflibercept, however, was reported to elicit better improvement in terms of BCVA, with a mean change of + 13.30 as reported by Xie et al.[40] In addition, Zhang et al.[39] meta-analysis showed that ranibizumab resulted in less CSMT reduction with a reported mean reduction around −14.67, which is significantly less than the reduction observed with brolucizumab in the present study. Similarly, CSMT mean reduction with aflibercept injection was around −33.76 in Xie et al. meta-analysis.[40] Thus, brolucizumab, as seen in the present analysis resulted in a significantly higher mean reduction of CSMT, suggesting higher efficacy in this regard. Nevertheless, these numbers are subject to patients group characteristics and baseline conditions; therefore, future prospective head-to-head randomized clinical trials are recommended to investigate these differences.

Regarding the safety of brolucizumab use, six patients had developed retinal vasculitis. Nevertheless, the majority of them had a favorable prognosis and complete remission. These findings are consistent with the findings of HAWK and HARRIER studies, which found that brolucizumab had an overall well-tolerated safety profile. In this article, the overall assessment demonstrated that the combined IOI (iritis and uveitis) was higher in the brolucizumab 6 mg group, which contradicts our findings. Four patients who had received a 3 mg dose of brolucizumab reported adverse ocular events, while only 2 patients with the 6 mg dose complained of such issue. This could be explained by the fact that one of the included studies in the analysis investigated the 3 mg dose only without comparison with 6 mg dose, which results in a larger sample size for 3 mg ocular side effects.[34] In addition, in KESTLER study,[23] the follow-up period was longer in patients received 3 mg brolucizumab compared to 6 mg brolucizumab (mean of 12.5 and 9.4 months respectively) which could lead to detection of more cases with ocular side effects.

Four of our included trials, on the other hand, were associated with no ocular vascular events, which is consistent with the findings provided by Hänsli et al..[36] IOI is a potential adverse effect of all anti-VEGF medications that have been observed in numerous prior research,[38,41,42] and it had been highlighted in the context of brolucizumab recently, particularly in nAMD patients.[43] The use of brolucizumab is a risk-benefit balance in nAMD patients since it has shown treatment benefits, and experts have attempted to devise criteria for patient selection for the use of brolucizumab for nAMD, highlighting risk factors such as female gender and Japanese ethnicity in which higher incidence of IOI was reported.[41,44,45] Nevertheless, in patients with DME, brolucizumab showed safer results, as demonstrated by the KITE and KRESTEL trials.[46] This could partly be explained by demographic differences between patients with DME and nAMD, especially since anti-brolucizumab antibodies were observed in patients who had never received the drug, suggesting a preexisting antibody that was linked to specific human-leukocyte antigen (HLA) subtypes.[29,47] Furthermore, Hirano, T. et al.[48] studied 23 eyes with DME who received brolucizumab in a Japanese population and reported that no patient had IOI. This variation in the safety profile of brolucizumab is yet under investigation. Recently, it has been suggested in the literature that DR and its progression are directly linked to an immunological dysregulation.[49] This goes in accordance with the findings of Busch et al., where DR patients had higher concentration of brolucizumab ADAs in DR patients, especially in vitreous samples compared to serum.[29] Despite this, IOI was reported more commonly with nAMD compared to DME following brolucizumab treatment. It is also possible that more patients with nAMD

received the medication compared to patients with DME, leading to a larger number of reports of adverse events from patients with nAMD. This should be further evaluated in future studies.

In our study, the mean (range) time to the event from the last brolucizumab was 115.67 (30–203) days, which is longer than the previous systematic review, which showed that the mean (range) time to the event from the last brolucizumab is 19.4 (0–63) days,[50] and also longer than the results of the HAWK and HARRIER study, which reported that the majority of IOI occurred within the first 12 weeks of treatment.[22] The main limitation of this review is the paucity of studies using brolucizumab in the treatment of DME or DR, with most results being driven by the two large RCTs. Since brolucizumab is a new medication, our understanding of its efficacy and safety profiles is yet to be deepened and refined. Our review sheds some light on the difference between both doses of brolucizumab with regards to the risk of ocular vascular adverse events. Furthermore, for unexplainable reasons, the risk of IOI associated with brolucizumab may be less when treating DME compared to wet AMD. These findings should be confirmed in future studies.

CONCLUSION

Brolucizumab is a relatively new anti-VEGF agent that has been used in the treatment of DME and DR. It showed great potential in improving BCVA and CSMT of patients with DME with the possibility of less frequent injections compared to other anti-VEGF agents. Brolucizumab safety was also assessed, and adverse effects were relatively few, most concerning of which are retinal vasculitis and retinal vascular occlusion, with possible less adverse events with the 6 mg dose vs the 3 mg and in DME patients vs nAMD patients that requires further studies.

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Authors' Contributions

Conceptualization: HAS, AA; Data curation: MJT, MTA, AA; Formal analysis: SI, LAS; Funding acquisition: HAS; Investigation: QAS, NA; Methodology: HAS, AGE, AA; Project administration: BA, AGE; Resources: MJT, MTA; Software; HAS, SI; Supervision: AGE, HAS, AA; Validation: MJT, MTA, AA; Visualization: LAS, NA; Roles/Writing - original draft: HAS, MJT, AGE, AA; Writing - review & editing: QAS, NA, HAS. All authors read and approved the final manuscript.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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