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Brolucizumab versus Aflibercept in Patients with Diabetic Macular Edema: A Meta-Analysis of Randomized Controlled Trials

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Purpose: To assess efficacy and safety of brolucizumab versus aflibercept in patients with diabetic macular edema (DME).

Patients and Methods: We performed a systematic review and meta-analysis with trial sequential analysis (TSA). We searched Embase, Cochrane Central Register of Controlled Trials and PubMed databases from inception to February 16, 2024 for randomized controlled trials (RCTs) comparing brolucizumab with aflibercept in patients with DME and reporting any of the visual, anatomical and safety outcomes of interest. We conducted a TSA of safety outcomes to assess the risk of statistical errors.

Results: 1253 patients (1253 eyes) from 3 RCTs were included, of whom 57% received brolucizumab and 43% received aflibercept. Mean follow-up ranged from 52 to 100 weeks. Brolucizumab was non-inferior to aflibercept when comparing the mean change of best-corrected visual acuity from baseline (least squares mean difference [LSMD] 0.29; 95% confidence interval [CI] −1.37 to 1.95; p = 0.73). Change in central subfield thickness was significantly greater in the brolucizumab group compared with aflibercept (LSMD −24.5 µm; 95% CI −48.2 to −0.7 µm; p < 0.05). Incidence of adverse events of special interest (AESIs) (risk ratio [RR] 1.7; p = 0.08) and incidence of ≥1 ocular adverse events (AEs) (RR 0.95; p = 0.45) were not significantly different between groups.

Conclusion: Brolucizumab was non-inferior in functional outcomes and was superior to aflibercept in anatomical parameters. Ocular AEs and AESIs were numerically low and not statistically significant. Our findings underscore the importance of new RCTs powered to assess safety outcomes in order to suggest brolucizumab as an alternative to the treatment of DME.

Keywords: brolucizumab, aflibercept, diabetic macular edema, anti-VEGF, diabetic retinopathy

Introduction

A total of 38.4 million people in the United States of America have diabetes, accounting for more than 11% of the population. [1] Diabetic macular edema (DME), a vision threatening complication, causes microvascular fluid, lipid and protein leakage into the macula[2] resulting in visual impairment and is the leading cause of vision loss in the adult working population.[3]

Current treatment modalities utilized in DME include anti-vascular endothelial growth factors (anti-VEGFs) intravitreal injections with frequent clinic assessments, resulting in high patient treatment burden and overall poor treatment adherence.[4] Besides socioeconomical constraints, which make the ongoing cost and frequency of injections burdensome, patients perceptions of perceived barriers, benefits, and susceptibility play a critical role, as those who underestimate the severity of DME or lack a supportive network are less likely to adhere to treatment regimens.[5] Therefore, the need for anti-VEGF therapies that increase duration between clinical visits, while providing anatomical and functional results is of great interest.

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Studies comparing real-world outcomes with randomized controlled trials (RCTs) show that patients who do not adhere to the recommended frequency of anti-VEGF injections experience inferior visual and anatomical outcomes. In clinical practice, patients typically receive fewer injections than those in RCTs, leading to less visual gain and higher central macular thickness over time.[6,7] This disparity underscores the need for consistent therapy to prevent progressive vision loss in DME.

One potential option for addressing these challenges is brolucizumab, a single-chain variable fragment with a high binding affinity for VEGF-A isoforms.[8,9] Its low molecular weight of 26 kDa allows for a molar dosing delivery 11 times higher than aflibercept.[8,9] In 2019, brolucizumab was approved for neovascular age-related macular degeneration (nAMD) treatment in more than 70 countries[10] however, due to concerning adverse events seen in post marketing case reports, the benefit-risk of brolucizumab has come into question.[11]

In two recent randomized control trials (RCTs) comparing brolucizumab with aflibercept in patients with DME, brolucizumab was found to have favorable anatomical and functional efficacy while maintaining an equal safety profile leading to authorization by the United States Food and Drug Administration (FDA) and the European Union (EU) for treatment of DME in 2022. In light of this new approval, we conducted a systematic review and meta-analysis comparing the efficacy and safety of brolucizumab with aflibercept.

Materials and Methods

Data Sources and Search Methods

We performed this systematic review and meta-analysis in accordance with the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines and registered our study in the International Prospective Register for Systematic Reviews (PROSPERO; CRD42024512576).[12]

We systematically conducted a search on Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed databases from inception to February 2024 for studies published in English with the following medical subject heading terms: "brolucizumab", "brolucizumab-dbll", "Beovu", "anti-VEGF", "anti-vascular endothelial growth factor", "aflibercept", "Eylea", "macular edema", "diabetic macular edema", "DME", "diabetic retinopathy", "diabetes mellitus" and "diabetes". Moreover, we analyzed the references of included publications for additional studies and contacted authors for unpublished data.

Eligibility Criteria

We included studies that met the following eligibility criteria: (1) randomized controlled trials comparing brolucizumab with aflibercept; (2) in patients with type 1 or type 2 diabetes; (3) with visual impairment due to diabetic macular edema; and (4) reporting any of the anatomical, visual and safety outcomes of interest – change from baseline in best-corrected visual acuity (BCVA); change from baseline in central subfield thickness (CST); fluid free macula; incidence of CST $<$ 280 μm; incidence of $\geq$ 1 ocular adverse events; and incidence of adverse events of special interest, which include intraocular inflammation, uveitis or endophthalmitis, retinal vasculitis and retinal vascular occlusion. We excluded nonrandomized studies and studies that included participants with macular edema due to retinal vein occlusion or neovascular age-related macular degeneration.

Data Extraction

Two authors (L.B.J. and G.B.J.) independently extracted relevant data following pre-defined search criteria, data extraction and quality assessment methods. Disagreements were resolved by consensus among three authors (L.B.J., G.B.J. and F.P.G).

Quality Assessment

Two independent authors (L.B.J. and G.B.J.) analyzed the risk of bias and quality assessment of individual studies with the Revised Cochrane Collaboration's tool for assessing risk of bias in randomized trials (RoB 2).[13] Any disagreement was solved via discussion. The RoB 2 tool ranks RCTs as having "high risk of bias", "low risk of bias", or "some

concerns" based on five domains. Due to the small number of included studies, we could not perform funnel plots of individual study weights against point estimates to assess publication bias.

Statistical Synthesis and Analysis

Statistics were analyzed with Review Manager 5.4 (Nordic Cochrane Centre, The Cochrane Collaboration). We compared treatment effects using pooled risk ratios (RRs) and least squares mean differences (LSMDs) with 95% confidence intervals (CIs) for dichotomous and continuous endpoints, respectively. Based on the 3 included studies, we considered change from baseline in BCVA to be noninferior when the lower limit of the 95% CI was greater than −4. Heterogeneity was assessed with Cochran Q test and I^2 statistics; p values of < 0.10 and $I^2 > 25\%$ were considered significant for heterogeneity. We used a fixed-effect model for endpoints with $I^2 < 25\%$ (low heterogeneity). In pooled outcomes with high heterogeneity, DerSimonian and Laird random-effects model was applied. P values of < 0.05 were considered statistically significant. Sensitivity analysis and funnel plots were not performed due to the small number of RCTs.

We conducted trial sequential analysis (TSA) of safety outcomes to assess the risk of type-1 and type-2 errors using the TSA Viewer 0.9.5.10 Beta (Copenhagen Trial Unit, 2016). The Z-curve (blue full line) represents the cumulative Z-score of the meta-analysis as each RCT is included. We utilized a 5% risk of type-1 error with a power of 80% to estimate the required information size. When the Z-curve did not cross any of the boundaries and the required information size had not been achieved, we concluded that more studies would be warranted.

Results

Study Selection

Our initial search yielded 2575 results (Figure 1). After excluding duplicate records and studies based on title and abstract, 56 publications were thoroughly scrutinized for the inclusion and exclusion criteria. A total of 1253 patients (1253 eyes) from 3 RCTs were included in the systematic review and meta-analysis, of whom 714 (57%) received brolucizumab and 539 (43%) received aflibercept.

The dosing regimens and the baseline characteristics of each study are detailed in Table 1. In the brolucizumab group, 48.5% of patients received injections every 4 weeks and 51.5% received a loading dose of 5 injections every 6 weeks, followed by one injection every 8 or 12 weeks. In the aflibercept group, 31.7% of patients received injections every 4 weeks and 68.3% received a loading dose of 5 injections every 4 weeks, followed by one injection every 8 weeks. Participants in the brolucizumab group received a mean of 11.0 ± 3.1 injections, while participants in the aflibercept group received a mean of 12.6 ± 3.0 injections during a follow-up that ranged from 52 to 100 weeks. Males accounted for 59.4% of the population in the brolucizumab group and 64.2% in the aflibercept group. Mean age ranged from 61.6 ± 10.5 years in the brolucizumab group to 62.2 ± 9.8 in the aflibercept group. Type 2 diabetes mellitus was present in 93% and 96% of participants in the brolucizumab and aflibercept arms, respectively. The mean BCVA letter score was 63.9 ± 10.5 in the brolucizumab group and 63.2 ± 12.0 in the aflibercept group. Patients receiving brolucizumab had a mean CST of 489.6 ± 135.4 μm, while patients receiving aflibercept had a mean CST of 489.9 ± 142.9 μm.

Visual Outcomes

The primary endpoint of the included studies was change from baseline in BCVA at 52 weeks. In our pooled analysis, brolucizumab was non inferior to aflibercept when comparing the mean change of BCVA from baseline (LSMD 0.29; 95% CI −1.37 to 1.95; p = 0.73; Figure 2A). This noninferiority was also observed when including results for treatment up to 100 weeks (LSMD 0.65; 95% CI −1.67 to 2.97; p = 0.58; Figure 2B). There was no statistically significant difference between those who received brolucizumab compared with aflibercept in the rate of patients who achieved BCVA of ≥ 84 letters or ≥ 5-letter gain (78.6% vs 74.8%; p = 0.43; Figure 2C), ≥ 10-letter gain (59.7% vs 56.6%; p = 0.42; Figure 2D) and ≥ 15-letter gain from baseline (44.3% vs 39.7%; p = 0.20; Figure 2E). While the results did not reach statistical significance, treatment effects favored brolucizumab in all three comparisons.

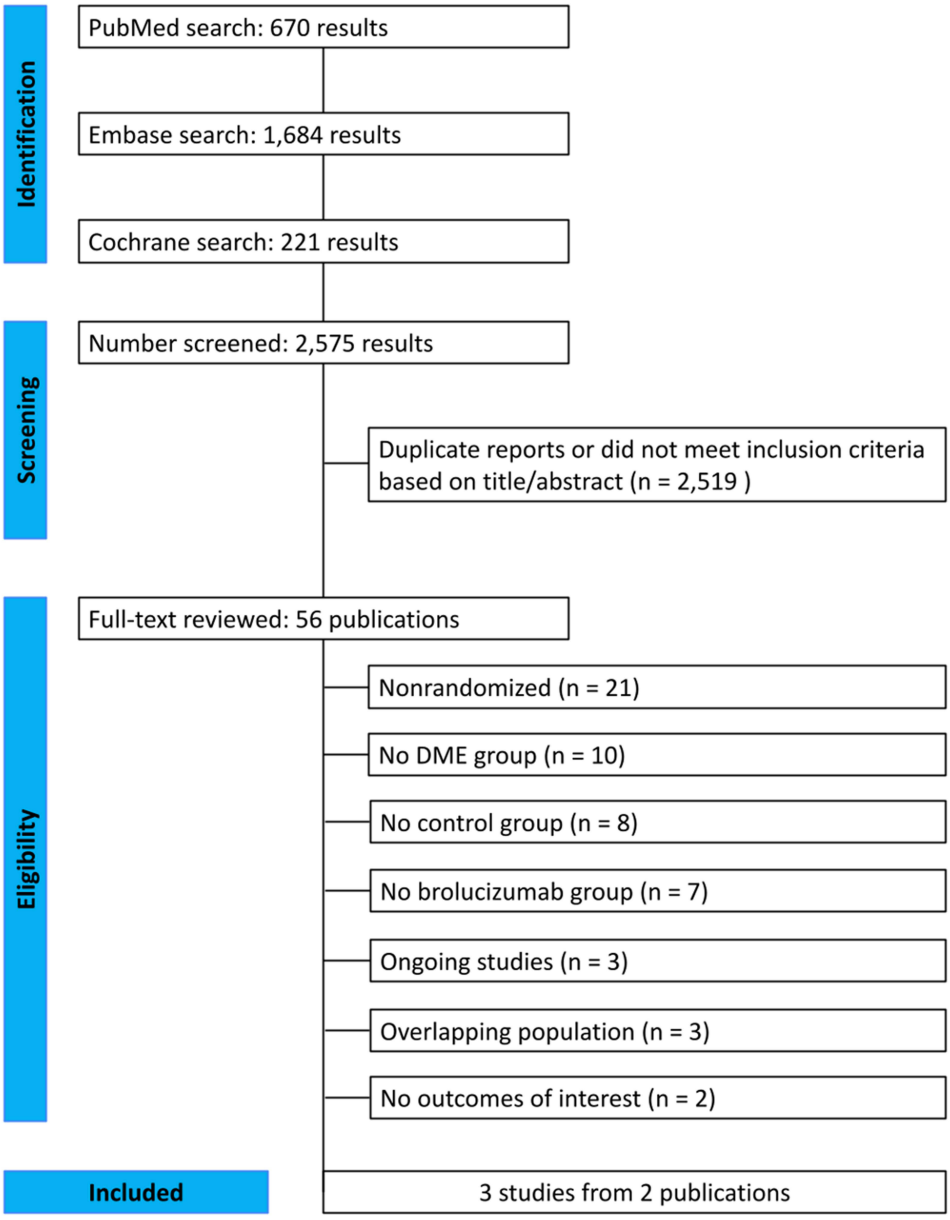

Figure 1 PRISMA flow diagram of study screening and selection.

Anatomical Outcomes

The change from baseline in CST at follow-up was significantly greater in brolucizumab patients (LSMD −24.5 μm; 95% CI −48.2 to −0.7 μm; $p < 0.05$; Figure 3A). Moreover, the proportion of patients with CST < 280 μm at follow-up was significantly higher in the brolucizumab group as compared with aflibercept (64.4% vs 46.9%; RR 1.37; 95% CI 1.17 to 1.60; $p < 0.001$; Figure 3B). There were no statistically significant differences in the proportion of patients with a fluid free macula (41.6% vs 44.9%; RR 1.00; 95% CI 0.59 to 1.72; $p = 0.99$; Figure 3C) nor with ≥ 2-step improvement in ETDRS (Early Treatment Diabetic Retinopathy Study) DRSS (Diabetic Retinopathy Severity Scale) score (37.5% vs 32.0%; RR 1.13; 95% CI 0.96 to 1.34; $p = 0.14$; Figure 3D).

Table 1 Baseline Characteristics of Included Studies

	Number of patients, No.	Anti-VEGF, No. (%)	Dosing regimen	Mean No. of injections ± SD	Males, No. (%)	Mean age, ± SD (years)	DM2, No. (%)	Mean HbA1c ± SD (%)	Mean BCVA letter score ± SD	Mean CST ± SD (μm)	Intraretinal fluid, No. (%)	Subretinal fluid, No. (%)	Follow-up (weeks)
KINGFISHER 2023[14]	517	BRO: 346 (66.9) AFL: 171 (33.1)	BRO: q4w AFL: q4w	BRO: 11.5 ± 2.7AFL: 11.6 ± 2.4	BRO: 194 (56.1) AFL: 105 (61.4)	BRO: 60.9 ± 10.6 AFL: 60.2 ± 9.3	BRO: 327 (94.5) AFL: 162 (94.7)	BRO: 7.8 ± 1.5 AFL: 8.0 ± 1.6	BRO: 61.3 ± 10.1 AFL: 60.5 ± 11.3	BRO: 514.1 ± 138.9 AFL: 511.2 ± 156.3	BRO: 344 (99.4) AFL: 170 (99.4)	BRO: 128 (37.0) AFL: 59 (34.5)	52
KESTREL 2023[15]	376	BRO: 189 (50.3) AFL: 187 (49.7)	BRO: 5x q6w + q12w or q8w AFL: 5x q4w + q8w	BRO: 10.6 ± 3.0 AFL: 13.0 ± 3.2	BRO: 110 (58.2) AFL: 126 (67.4)	BRO: 62.4 ± 10.1 AFL: 63.9 ± 10.1	BRO: 177 (93.7) AFL: 181 (96.8)	BRO: 7.7 ± 1.1 AFL: 7.4 ± 1.1	BRO: 66.6 ± 9.7 AFL: 65.2 ± 12.4	BRO: 453 ± 123 AFL: 476 ± 136	BRO: 189 (100) AFL: 184 (98.4)	BRO: 62 (32.8) AFL: 61 (32.6)	100
KITE 2023[15]	360	BRO: 179 (49.7) AFL: 181 (50.3)	BRO: 5x q6w + q12w or q8w AFL: 5x q4w +q8w	BRO: 10.3 ± 2.8 AFL: 13.2 ± 3.1	BRO: 120 (67.0) AFL: 115 (63.5)	BRO: 62.3 ± 10.6 AFL: 62.2 ± 9.5	BRO: 160 (89.4) AFL: 174 (96.1)	BRO: 7.6 ± 1.2 AFL: 7.5 ± 1.2	BRO: 66.0 ± 10.8 AFL: 63.7 ± 11.7	BRO: 481 ± 132 AFL: 484 ± 135	BRO: 176 (98.3) AFL: 179 (98.9)	BRO: 56 (31.3) AFL: 67 (37.0)	100
Total	1253	BRO: 714 (57) AFL: 539 (43) Total: 1253 (100)	BRO: 346 (48.5) q4w; 368 (51.5) 5x q6w + q12w or q8w. AFL: 171 (31.7) q4w; 368 (62.3) 5x q4w + q8w	BRO: 11.0 ± 3.1 AFL: 12.6 ± 3.0 Total: 11.7 ± 3.0	BRO: 424 (59.4) AFL: 346 (64.2) Total: 770 (61.5)	BRO: 61.6 ± 10.5 AFL: 62.2 ± 9.8 Total: 61.9 ± 10.2	BRO: 664 (93.0) AFL: 517 (95.9) Total: 1181 (94.3)	BRO: 7.7 ± 1.3 AFL: 7.6 ± 1.3 Total: 7.7 ± 1.3	BRO: 63.9 ± 10.5 AFL: 63.2 ± 12.0 Total: 63.6 ± 11.1	BRO: 489.6 ± 135.4 AFL: 489.9 ± 142.9 Total: 489.7 ± 138.7	BRO: 709 (99.3) AFL: 533 (98.9) Total: 1242 (99.1)	BRO: 246 (34.5) AFL: 187 (34.7) Total: 433 (34.6)	

Abbreviations: AFL, aflibercept 2 mg; BCVA, best-corrected visual acuity; BRO, brolucizumab 6 mg; CST, central subfield thickness; DM2, diabetes mellitus type 2; HbA1c, hemoglobin A1c; No, number of patients; q4w, injection every 4 weeks; q6w, injection every 6 weeks; q8w, injection every 8 weeks; q12w, injection every 12 weeks; SD, standard deviation; VEGF, vascular endothelial growth factor.

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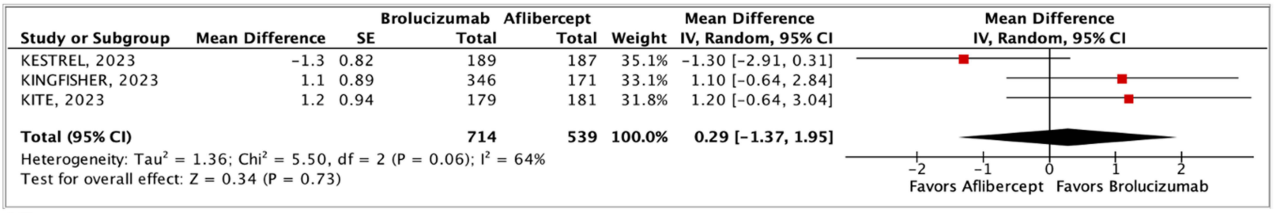
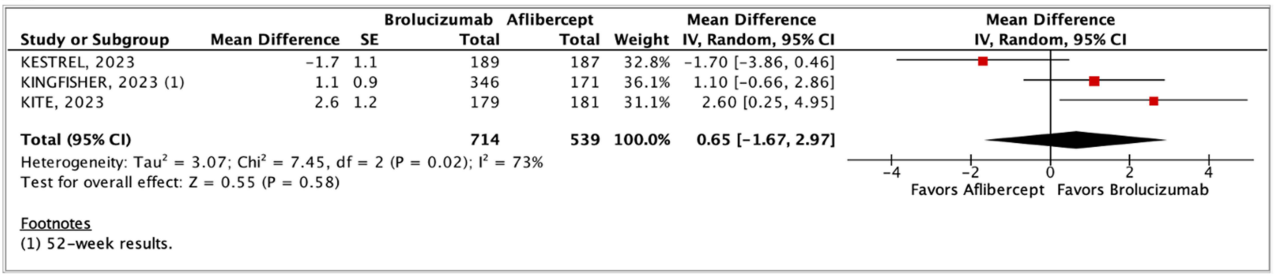
2A



2B



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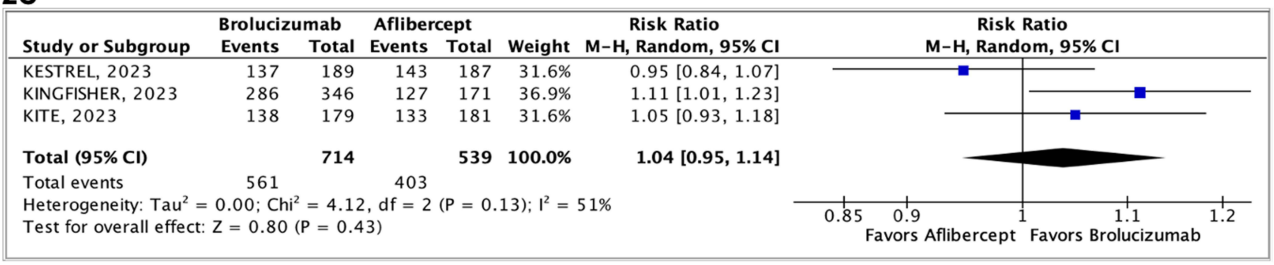

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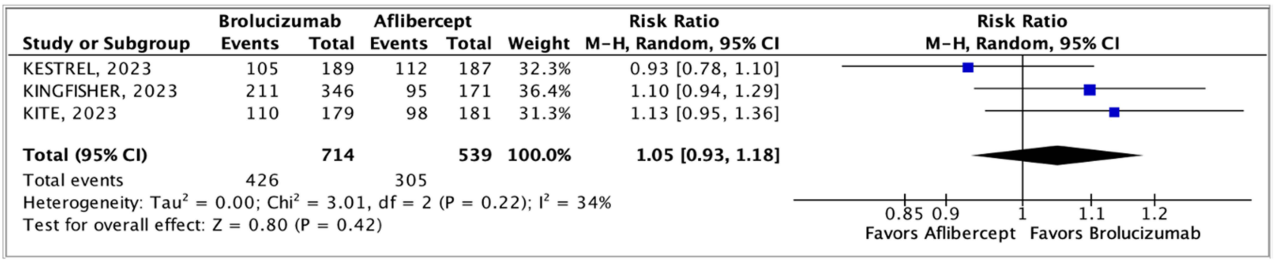


2E

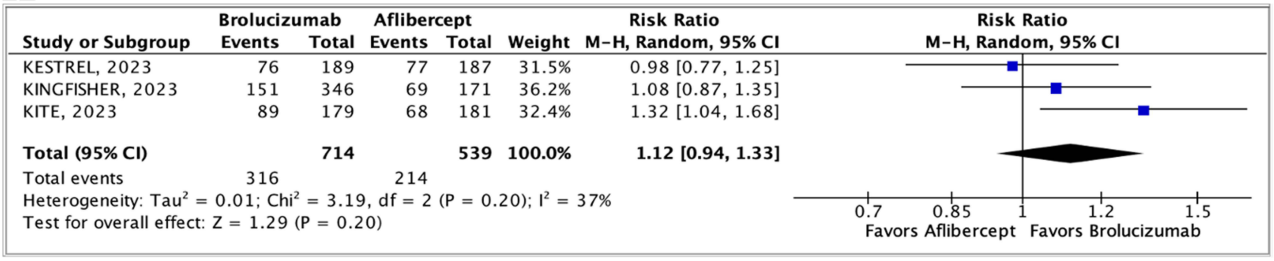


Figure 2 Visual outcomes. (**A**). Change from baseline in BCVA was noninferior in the brolucizumab relative to aflibercept at 52 weeks. (**B**). Change from baseline in BCVA was noninferior in the brolucizumab relative to aflibercept at 100 weeks. (**C**). There was no statistically significant difference in the proportion of patients with ≥ 5- letter gain from baseline or BCVA of ≥ 84 letters at follow-up between groups. (**D**). There was no statistically significant difference in the proportion of patients with ≥ 10- letter gain from baseline or BCVA of ≥ 84 letters at follow-up between groups. (**E**) There was no statistically significant difference in the proportion of patients with ≥ 15- letter gain from baseline or BCVA of ≥ 84 letters at follow-up between groups.

Safety Outcomes

Ocular adverse events were reported in 37.8% of patients who underwent brolucizumab therapy and in 42.1% of those undergoing aflibercept therapy with no statistical significance noted (RR 0.95; 95% CI 0.83 to 1.09; p = 0.45; Figure 4A). TSA indicated that 30.8% of the required information size had been reached and the cumulative Z-curve had not crossed

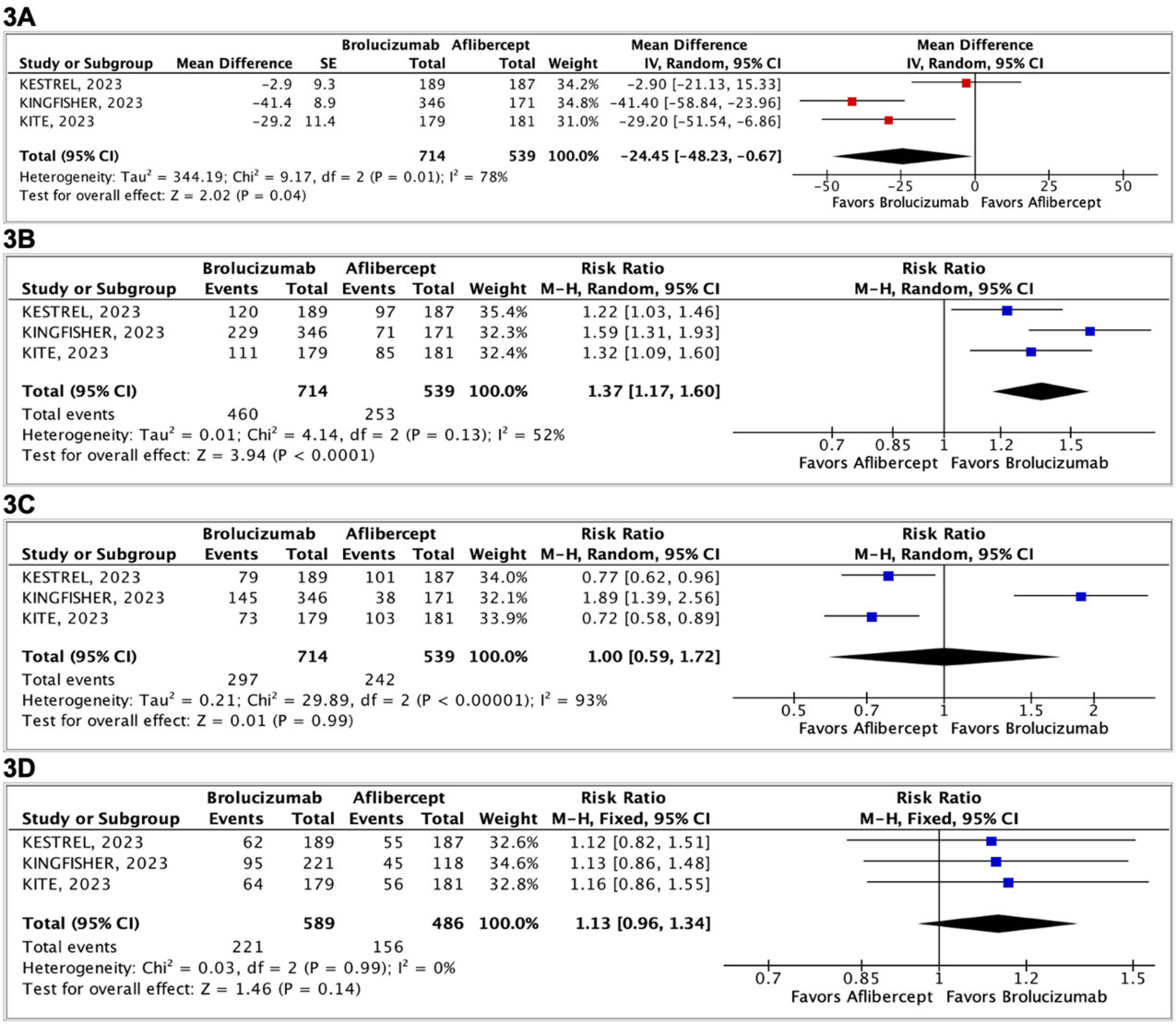


Figure 3 Anatomical outcomes. (**A**). Change from baseline in CST was significantly greater in the brolucizumab group relative to aflibercept (μm). (**B**). The proportion of patients with CST > 280 μm at follow-up was significantly greater in the brolucizumab group relative to aflibercept. (**C**). There was no statistically significant difference in the proportion of patients with fluid free macula at follow-up between groups. (**D**). There was no statistically significant difference in the proportion of patients with ≥ 2-step improvement in ETDRS DRSS score at follow-up between groups.

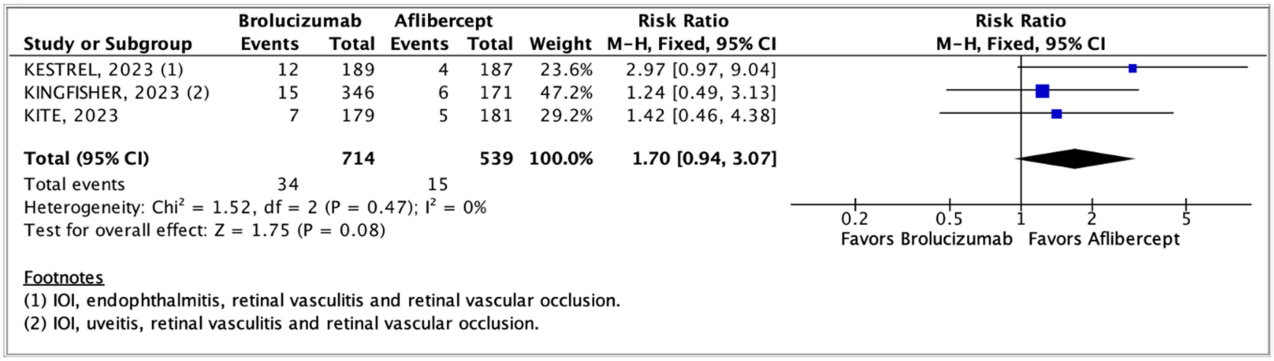
the conventional, monitoring or the futility boundaries (eFigure 1A), therefore, the included trials did not provide sufficient evidence to determine a significant difference between rates of ocular adverse events between brolucizumab and aflibercept.

Adverse events of special interest reported in the RCTs included intraocular inflammation, uveitis or endophthalmitis, retinal vasculitis and retinal vascular occlusion. There was no statistically significant difference between brolucizumab and aflibercept (4.8% vs 2.8%; RR 1.7; p = 0.08; Figure 4B) for these adverse events reported. The cumulative Z-curve corresponded to 43.1% of the required information size and did not cross any of the boundaries (eFigure 1B). Thus, there was insufficient data to conclude the greater incidence of AESIs in the brolucizumab group as compared with aflibercept is of statistical significance.

Intraocular inflammation was the most commonly reported adverse event, however there was no statistically significant difference between the brolucizumab and aflibercept arms (3.6% vs 1.9%; RR 1.82; p = 0.10; Figure 4C). TSA indicated that the pooled IOI events accounted for 47.6% of the required information size. The cumulative Z-curve

4A

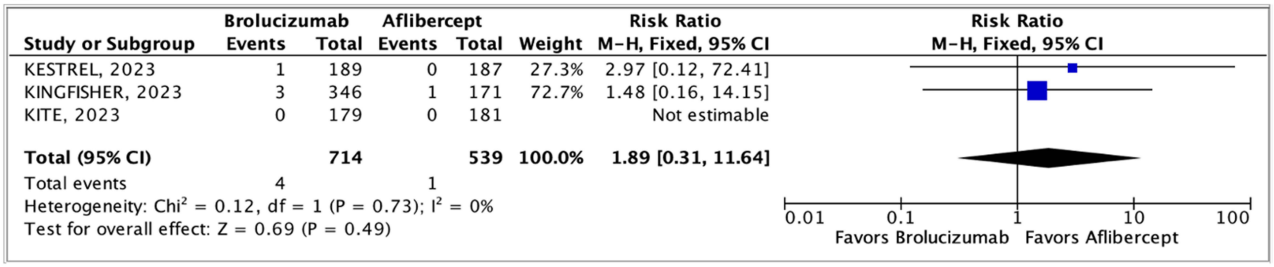
4B



Footnotes
(1) IOI, endophthalmitis, retinal vasculitis and retinal vascular occlusion.
(2) IOI, uveitis, retinal vasculitis and retinal vascular occlusion.

4C

4D



4E

Figure 4 Safety outcomes. (**A**). There was no statistically significant difference in the incidence of ocular adverse events between groups. (**B**). There was no statistically significant difference in the incidence of adverse events of special interest between groups. (**C**). There was no statistically significant difference in the incidence of intraocular inflammation between groups. (**D**). There was no statistically significant difference in the incidence of retinal vasculitis between groups. (**E**). There was no statistically significant difference in the incidence of retinal vascular occlusion between groups.

did not reach the conventional, monitoring or futility boundaries (eFigure 1C). Additional studies are needed to accept or reject the overall test effect.

Retinal vasculitis occurred in 0.6% and 0.2% of patients receiving brolucizumab and aflibercept injections, respectively, with no statistically significant difference observed (RR 1.89; p = 0.49; Figure 4D). The cumulative Z-curve did not reach the required information size on TSA. None of the boundaries were crossed (eFigure 1D). Therefore, more studies are warranted to accept or reject the overall test effect.

Retinal vascular occlusion was reported in 0.7% of patients in the brolucizumab group and in 0.6% of the aflibercept group, with no statistically significant difference between both arms (RR 1.39; p = 0.64; Figure 4E). We were not able to perform trial sequential analysis due to the small number of events.

Risk of Bias

Quality appraisal of each RCT is detailed in eTable 1. Overall, studies were classified as low for the risk of bias.

Discussion

In this systematic review and meta-analysis of 3 RCTs including 1253 patients (1253 eyes) with DME, we found that: (1) CST was approximately 25 μm lower in patients who received brolucizumab relative to aflibercept ($p < 0.05$); (2) brolucizumab was noninferior to aflibercept in change from baseline in BCVA at 52 (LSMD 0.29; 95% CI −1.37 to 1.95) and 100 weeks (LSMD 0.65; 95% CI −1.67 to 2.97); and (3), there was no statistically significant difference in the rate of ocular adverse events of special interest as compared with aflibercept (4.8% vs 2.8%, respectively; p = 0.08).

Intravitreal anti-VEGF injections have replaced laser photocoagulation as the standard of care for diabetic macular edema.[16] Ever since, DME treatment has relied on frequent clinical visits to assess disease activity and multiple anti-VEGFs injections with treatment intervals ranging from monthly dosing to injections every 8 to 16 weeks.[17–19] This creates considerable patient treatment burdens and healthcare system expenditures.[20] Moreover, the multiple comorbidities often seen in DME patients contribute to low adherence rates, premature discontinuation of treatment, and subsequently undertreatment and suboptimal results.[4,21] Therefore, brolucizumab with its initial every 6 week dosing as compared with aflibercept given at 4 week intervals, may prove helpful in improving patient adherence, reducing treatment burdens and ultimately leading to improved visual outcomes/reduction in visual morbidity.[14,15]

Although KINGFISHER implemented a non-approved dosing regimen for brolucizumab (q4w), its inclusion in our study provided valuable insights into its outcomes. Despite the increased mean number of injections at 52 weeks (11.5 ± 2.7 in KINGFISHER versus 6.8 ± 1.2 and 7.0 ± 1.3 in KESTREL and KITE, respectively), the incidence of AESIs was comparable between the regimens (4.3% in KINGFISHER versus 3.8% in KESTREL and KITE). Notably, anatomical and visual outcomes were more favorable with more frequent dosing; KINGFISHER achieved a greater reduction in CST from baseline compared with aflibercept (−41.4 μm versus −15.2 μm in KESTREL and KITE) and a slightly better BCVA change from baseline at 52 weeks (1.1 letters versus −0.1 letter in KESTREL and KITE, both non-inferior to aflibercept). These findings suggest that more frequent dosing may provide enhanced anatomical and visual benefits without substantially raising AESI risks, supporting an individualized approach where dosing can be tailored to the patient's specific clinical needs.

In our meta-analysis, brolucizumab led to better anatomical outcomes as only 35.6% of patients maintained CST values > 280 μm at follow-up as compared with 53.1% in the aflibercept group ($p < 0.001$). In a post-hoc analysis of the Protocol I, persistent DME led to worse visual improvements. Additionally, subjects with a higher number of clinical visits presenting with persistent edema (> 250 μm) gained 4 to 6 less ETDRS letters in 3 years of follow-up in comparison with the better responders[22] highlighting that despite minimal initial changes in BCVA, favorable anatomical changes may lead to long-term improvements in visual outcomes if not at very least preservation of visual acuity.[23]

Brolucizumab, initially approved for treatment of nAMD, has demonstrated a potent drying effect in treating patients with intra and subretinal fluid while improving BCVA,[10] however its widespread use has been limited given safety concerns, namely increased incidence of intraocular inflammation (IOI) leading to retinal vasculitis (RV) or retinal vascular occlusion (RVO).[11] Results from the MERLIN trial as well as early case reports demonstrated IOI in 9.3% of patients treated with brolucizumab (4.5% with aflibercept) with incidence rates of RV (0.8%) and RVO (2.0%). In

contradistinction, there were no reported cases of RV or RVO in patients treated with aflibercept.[11,24,25] These findings led to the early termination of several clinical trials and gave clinicians pause when deciding between which anti-VEGF agent to use for their nAMD patients.[11]

Numerous hypotheses have been formulated to explain the higher rates of IOI. Among these is the smaller molecular size of brolucizumab that could stimulate a stronger local immune reaction.[26] Several risk factors may contribute to worse safety outcomes, such as silicone oil residue, endotoxins, bilateral anti-VEGF injections and female sex.[27–29] In our meta-analysis, despite AESIs being numerically greater in the brolucizumab arm compared with aflibercept (4.8% vs 2.8%; p = 0.08), none of the findings on safety endpoints were statistically significant. In addition, both retinal vasculitis and retinal vascular occlusion events were reported in a nominal percentage of patients in the brolucizumab and aflibercept groups, with comparable rates (0.6% vs 0.2%, respectively; 0.7% vs 0.6%, respectively). The q4w dosing interval from KINGFISHER (as opposed to q6w with treat and extend protocol seen in other studies) may have contributed to the absence of statistical significance in our pooled safety outcomes. Thus, results within this meta-analysis suggest that, similarly to MERLIN, brolucizumab might be responsible for an increased incidence of adverse events not only among patients with nAMD, but also with DME. However, data from the TSA reinforces that conclusions based on our findings should be taken with caution. Notably, the sequential analysis ruled out potential risk of type-2 errors. Additionally, it demonstrated that, although numerically higher in the intervention group, the incidence of adverse events represented by the Z-curve has not reached the futility boundary yet, allowing further investigations with RCTs powered to assess safety outcomes in this population.

Real-World Evidence (RWE) provides valuable insights into the safety profiles of brolucizumab and aflibercept under routine clinical conditions. The retrospective BRADIR study analyzed brolucizumab and aflibercept over a 52-week period and reported subconjunctival hemorrhage in 10% of 30 eyes treated with brolucizumab and 14.3% of 28 eyes treated with aflibercept (p = 0.7), with no additional ocular or systemic adverse events, including IOI, in either group.[30] Similarly, the study by Rübsam et al, which included 175 intravitreal injections of brolucizumab over 9 months, found no serious adverse events, including no cases of IOI or retinal vasculitis.[31] Moreover, a one-year real-life case series involving 45 treatment-naive eyes randomized to brolucizumab or aflibercept treatment reported no ocular complications at follow-up.[32] While these RWE findings suggest a low incidence of inflammation-related events in real-world practice, the relatively short follow-up periods and limited sample sizes underscore the need for more RWE studies and continued monitoring to fully assess the long-term incidence of adverse events of special interest.

In deciding between brolucizumab and aflibercept for DME, patient-specific criteria play a crucial role. Brolucizumab may be well-suited for patients with severe or persistent fluid accumulation, as it has demonstrated significant anatomical improvements, such as reductions in retinal thickness and fluid levels.[15] Additionally, the potential for extended dosing intervals, up to 12 weeks in some cases, offers a reduced treatment burden, making it an option for patients facing challenges with frequent clinic visits due to socioeconomic constraints or adherence issues.[10,15] In contrast, aflibercept may be an appropriate choice for patients with a history of inflammatory responses to anti-VEGF agents or those with less aggressive disease presentations where moderate fluid control is adequate.[10,11,15,33]

Our study has several limitations. Although the KINGFISHER trial compared brolucizumab with aflibercept in a head-to-head approach, the applied treatment interval (every 4 weeks) is not approved by either the FDA or the EU. Current package labeling indicates brolucizumab should be dosed at 6 weeks intervals for the first 5 doses followed by extension to 8 to 12 weeks. Thus, results of this study may not apply to real-world practice patterns and therefore limit external validity. Of the included studies only 2 RCTs evaluated outcomes after the 52-week period which may not capture the full treatment effect or long-term efficacy and safety of this anti-VEGF therapy, given that DME is a chronic condition that often requires prolonged treatment and monitoring. Additionally, in the KESTREL and KITE studies, patients in the brolucizumab receiving injections every 8 weeks were not allowed to extend the treatment interval to 12 weeks. This inflexibility of treatment interval extension may also limit external validity as it does not reflect individual prescriber preferences for treat and extend protocols. Although our meta-analysis did not find statistically significant differences in safety outcomes, KESTREL and KITE were not powered to assess these endpoints. Despite having included 1253 eyes, we were not able to perform sensitivity analysis due to the low number of RCTs, which limited the evaluation of the effects of heterogeneity on the pooled outcomes. Finally, the absence of patient-level data in the

included RCTs precluded subgroup analyses, such as the difference in the incidence of adverse events of special interest between genders, age categories and ethnicities.

Conclusion

In conclusion, our study showed that, despite noninferiority to aflibercept in terms of functional outcomes, brolucizumab significantly improves anatomical parameters of patients with DME. In contrast to previous studies comparing both anti-VEGFs therapies, our meta-analysis did not find statistically significant differences in ocular adverse events between groups (including retinal vasculitis or retinal vascular occlusions). Although having included more participants than previous studies, our findings, supported by TSA, underscore the importance of new RCTs powered to assess safety outcomes in order to suggest brolucizumab as an alternative to the current treatment of DME.

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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.

Disclosure

All authors declare no financial support nor conflicts of interest in this work.

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