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BROLUCIZUMAB FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION IN REAL-WORLD SETTING: A SYSTEMATIC REVIEW

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Abstract

Introduction: The mainstay treatment for neovascular AMD (nAMD) is intravitreal injections of anti-vascular growth factor (anti-VEGF) agents. Based on clinical trials, a newly developed anti-VEGF named brolucizumab showed noninferiority in anatomical and functional outcomes with longer injection interval, when compared to previous anti-VEGF agents; however, severe post-injection inflammation has been observed. This review aims to evaluate the efficacy and safety of brolucizumab in real-world clinical setting.

Methods: We conducted systematic searches in Pubmed, Science Direct, Clinicalkey, and Scopus. Observational studies, case series, and individual case studies enrolling naïve-treatment and switch-therapy nAMD patients who received intravitreal injection of brolucizumab were eligible for this review.

Result: We included 12 studies, comprising 772 patients and 848 eyes, that reported the outcome of intravitreal injection of brolucizumab in real-world practice. The mean age of patients was 77 years old. Follow-up period ranged from 7,2 weeks to 52 weeks. Improvement in visual acuity was mostly observed in treatment-naïve groups, ranging from +4,5 to +11,9 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. Improvement in retinal thickness and reduction in retinal fluids were reported in both groups, with mean central retinal thickness (CRT) change of 94,92 µm. Significant reductions of subretinal fluid (SRF) were observed in 4 studies, intraretinal fluid (IRF) in 2 studies, and pigment epithelial detachment (PED) in 3 studies. Eight studies reported injection interval, the longest of which extended to 12 weeks. Inflammatory events following brolucizumab injection were reported in 8,01% of eyes, ranging from mild to severe inflammation, with 34,2% of the intraocular inflammation occurring in the vitreous (22 eyes). Brolucizumab may help alleviate treatment burden in real-world clinical setting by reducing disease activity, mainly demonstrated as improvement in retinal thickness, reduction in retinal fluid, and prolongation of injection interval. Clinicians must be aware of the possible inflammatory events following brolucizumab injection.

Keywords: Brolucizumab, efficacy, intraocular inflammation, neovascular age-related macular degeneration, real-world study, safety

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INTRODUCTION

Age-related macular degeneration (AMD) is a chronic, degenerative eye disease that causes pathological changes to the deep retinal layers of the macula and surrounding vessels, eventually resulting in loss of central vision.[1] It is the leading cause of blindness in elderly people. Advanced neovascular AMD (nAMD), or wet AMD, is characterized by choroidal neovascularization in either eye.[1] This neovascularization may result in hemorrhage and leakage of fluid in inner blindness if no treatment is instigated. The global prevalence of AMD is estimated to be 8.69% of the population.[2] While nAMD only accounts for 10-20% of the AMD patients, it is the most devastating form of AMD that is responsible for the vision loss in AMD patients.[1–3]

The main pharmacological treatment for nAMD mainly involves intravitreal injections of anti-vascular growth factor (anti-VEGF) agents, namely pegaptanib sodium, bevacizumab, ranibizumab, and aflibercept.[4] The mechanism of action of anti-VEGF for nAMD is through inhibition of capillary leakage and growth of choroidal neovascularization.[5] Unfortunately, there are still unmet needs in nAMD treatments. Based on real-world data, many patients do not receive full loading dose and are not frequently monitored, compared to treatment standards set by the clinical trials.[6,7] Not only due to patient's compliance, access to healthcare and health insurance contribute to this issue, too. Relatively short acting duration of the currently used anti-VEGF also results in repeated treatments, hence higher costs in patients.[8]

There is a newly developed anti-VEGF agent named brolucizumab, a humanized, monoclonal single-chain Fv antibody fragment inhibitor of VEGF-A.[9,10] It binds with high affinity to isoforms of VEGF-A, hence binding of VEGF-A to its receptors is prevented. Single-chain fragments are smaller in size with less crystallizable domain.[11] Because of these characteristics, brolucizumab has a bigger distribution, better penetration, and longer period of concentration in the human eyes, compared with the previous anti-VEGF, so that it may be a more durable agent for nAMD patients. [9,10] Based on data from the clinical trials, brolucizumab was noninferior to aflibercept in terms of both visual and anatomic outcomes.[10] Although it has been approved for usage by the Food and Drugs Administration (FDA), there are some adverse events that have been observed in patients after receiving brolucizumab, such as severe intraocular inflammation and retinal vasculitis.[2]

We review the existing evidence to evaluate the efficacy and safety of brolucizumab in nAMD in real clinical experiences through real-world studies.

METHODS

Literature search

Literature search was conducted on February 12, 2023, through online databases, namely Pubmed, Clinicalkey, Science Direct, and Scopus, as well as secondary search through reference list. The keywords for the literature search included the combination of "brolucizumab", "boevu", "age-related macular degeneration", "wet age-related macular degeneration", "neovascular age-related degeneration", and "real-world" with Booelan operators.

Eligibility criteria

The studies included in this review conformed to a few inclusion criteria. We only included available full-text articles published within the last 5 years (from 2018 to 2023) that are written in English. All real-world studies enrolling neovascular AMD patients who received intravitreal injection of

brolucizumab in 6 mg dosing, including naïve-treatment and switch-therapy patients, were eligible for this systematic review. Limitations regarding study type were not implemented. Observational studies, case series, and individual case studies were allowed to be included. Articles on clinical trials, commentary, editorial articles, and conference reports were excluded.

Study selection and analysis

Following the literature search, the results were then screened by the evaluation of titles, abstracts, and/or full text. We then selected the relevant literature, retrieved the full text articles that met the criteria or for doubtful eligibility from titles and abstracts, and extracted the data required. Two reviewers independently assessed the full-text studies for this review.

Outcome measures

Primary outcome of this study is the efficacy based on changes in best-corrected visual acuity (BCVA); changes in central retinal thickness (CRT), subretinal fluid (SRF), intraretinal fluid (IRF), and pigment epithelial detachment (PED); interval of injections; as well as the safety of brolucizumab determined by adverse events, classified as intraocular inflammation (IOI) and non-inflammation.

RESULT

Literature search results

We conducted a literature search through several databases, namely Pubmed, Clinicalkey, Science Direct, and Scopus. The literature selection process retrieved 160 original abstracts, of which 42 met the inclusion criteria. After full text reviews, four studies were excluded because of duplication and the remaining 12 studies were included in the final appraisal and review. One previous systematic review on this specific issue was identified during the process. The literature search and selection process are shown in Figure 1.

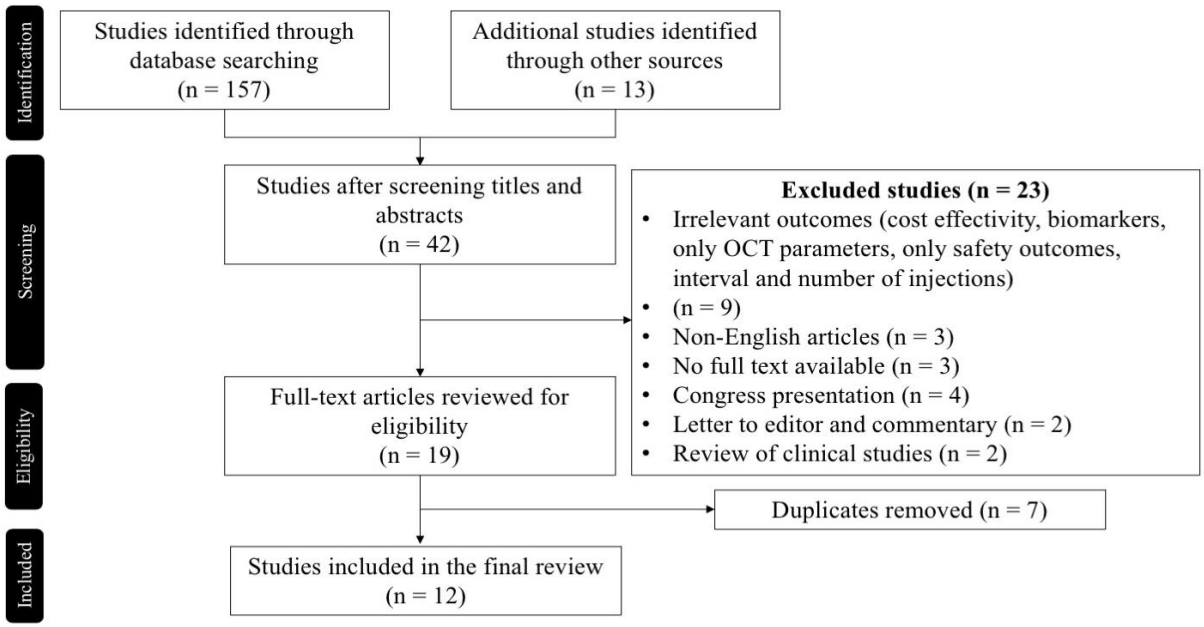

Figure 1. Literature search and selection flowchart

Validity assessment

Validity assessment of the articles was performed using Assessment of Real-World Observational Studies (ArRoWS) critical appraisal tool, shown in the additional data in this paper.

Study characteristics

The overview of studies included in this review was summarized in Table 1. We included 12 studies, comprising a total of 772 patients and 848 eyes, that reported the outcome of intravitreal injection of 6mg of brolucizumab in real-world practice. All studies included were retrospective, observational studies, so that they are categorized into level II studies based on the Oxford Center of Evidence Based Medicine 2011 Level of Evidence. More than half of the studies were multicenter studies (seven studies). These studies were conducted in various countries, namely United States of America (USA), Germany, Switzerland, Japan and India. Most studies enrolled switch therapy patients (six studies), while two studies included only treatment-naïve patients and four others recruited both types of patients. The mean age of patients was 77 years old. More than half of the patients were females (50.2%). The median follow-up period was 30,98 weeks, with the shortest period being 7,2 weeks and the longest being 52 weeks

Table 1. Characteristics of the included studies

Author	Year	Study type	Country (setting)	Type of patients	Patients (n)	Eyes (n)	Treatment-naïve / switch therapy eyes	Mean age	Follow-up period	Key results	Reason for switch therapy	Previous anti-VEGF used
Bilgic et al (PROBE)	2021	Retrospective, observational	India (multicenter)	Treatment-naïve patients	27	27	27/0	65,1 years	11,2 months	PRN brolucizumab therapy is effective in treatment-naïve patients in the first year of treatment.	NA*	NA*
Tanaka et al	2022	Retrospective, case control study	Japan (multicenter)	Treatment-naïve patients	57	58	58/0	74.2 ± 6.6 years	3 months	Brolucizumab therapy improved VA, reduced CRT, with high fluid resolution rate and polypoidal lesion regression, with 14% chance of IOI development.	NA*	NA*

Bulirsch et al	2021	Retrospective, observational	Germany (monocenter)	Switch therapy patients	57	63	0/63	79.5±6.7 years	16.04 ± 6.86 weeks	Switch to brolucizumab may be an option in nAMD patients that respond poorly to other anti-VEGF agents, in which it specifically shows beneficial morphological effect	Recalcitrant fluid accumulations on OCT	Ranibizumab, aflibercept and bevacizumab
Abdin et al	2022	Retrospective, observational	Germany (monocenter)	Switch therapy patients	19	21	0/21	76 ± 8 years	52 weeks	Brolucizumab improved anatomic outcomes, particularly reducing SRF and PED, and subsequently CMT.	Presence of IRF and/or SRF and/or PED despite treatment with at least anti-VEGF	Ranibizumab, aflibercept, and bevacizumab
Haensli et al	2021	Prospective open-label, cohort	Switzerland (monocenter)	Switch therapy patients	12	12	0/12	80.31 years	6 months	Brolucizumab showed improvement in reading visual acuity and longer treatment interval of injection, adverse effects of IOI were encountered.	MNV activity as confirmed by dye leakage in FA and persistant fluid in OCT	Ranibizumab, aflibercept
Giunta et al	2022	Retrospective, observational	Canada (multicenter)	Switch therapy patients	73	73	0/73	78.9 years	28 weeks	Brolucizumab therapy resulted in morphological improvement (mean CRT and reduction in macular fluid) with longer injection interval in switch therapy patients.	Inability to extend treatment interval, persistent fluid	NA
Coney et al	2023	Retrospective, observational	USA (monocenter)	Switch therapy patients	154	174	0/174	80.5 years	12 months	Brolucizumab prolongs injection interval with maintenance of vision and reduction of CMT, compared to previously used anti-VEGF in switch-therapy patients.	NA	NA
Sharma et al	2020	Retrospective consecutive, interventional, uncontrolled study	USA (multicenter)	Switch therapy patients	42	42	0/42	79.2 ± 7.0 years	7,2 ± 3,6 weeks	Brolucizumab was effective in stabilizing VA and reducing retinal fluids. No IOI was reported in short period of study.	NA	Bevacizumab, ranibizumab, and aflibercept

Bilgic et al (REBA)	2021	Retrospective, observational	Germany and India (multicenter)	Switch therapy and treatment-naïve patients	78	105	25/80	69,2 years	10,4 months	Brolucizumab is effective for therapy in both naive-treatment and switch-therapy patients, with small and definite risk of developing IOI.	Recurrent, recalcitrant disease; inability to extend the interval beyond 4 weeks.	Aflibercept
Montesel et al	2021	Retrospective, observational	Switzerland (monocenter)	Switch therapy and treatment-naïve patients	19	19	4/15	78 ± 8.4 years	14.4 ± 9.0 weeks	Brolucizumab was able to reduce retinal fluids and stabilize the visual acuity, safety profile needs further investigation.	Persistent, active exudation after at least three other anti-VEGF injections	Ranibizumab, aflibercept
Chakraborty et al	2022	Retrospective consecutive, interventional, uncontrolled, nonrandomized study	India (multicenter)	Switch therapy and treatment-naïve patients	82	82	17/65	67.55 ± 10.25 years	52 weeks	Pro re nata brolucizumab therapy resulted in excellent visual outcomes, fluid resolution and retinal thickness reduction in both naive-treatment and switch therapy patients, with lower frequency of injections and majority of adverse events being mild.	Worsening or persistent CRT (<100µm reduction) despite repeated doses of previous anti-VEGF	Ranibizumab or aflibercept
Enríquez et al	2020	Retrospective case series	USA (multicenter)	Switch therapy and treatment-naïve patients	152	172	6/166	80.0 years	24 weeks	Brolucizumab resulted in stable VA and reduced CST in switch therapy eyes. IOI developed in 8.1% eyes, half of which were self-resolving.	Persistent fluid	Ranibizumab, aflibercept

CMT: central macular thickness; CRT: central retinal thickness; CST: central subfield thickness; IOI: intraocular inflammation; MNV: macular neovascularization, NA*: not applicable; NA: not available; OCT: optical coherence tomography; PED: pigment epithelial detachment; PRN: pro re nata; SRF: subretinal fluid; VA: visual acuity

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Study results

The primary outcome of the review is the efficacy of brolucizumab in real-world practice, as evaluated by BCVA, CRT, presence of retinal fluids (IRF, SRF, and PED), injection interval, as well as adverse events (both IOI and non-inflammation).

1. Functional marker

   The BCVA was measured as the functional marker in this study, using early treatment diabetic retinopathy (ETDRS) visual acuity chart in seven studies, while logMAR results from other five studies were then converted to ETDRS letters for analysis. Mean baseline BCVA was 57,71 letters and it was 68,74 at last follow-up. The changes in visual acuity observed in each study after the administration of intravitreal brolucizumab is shown in Table 2.

Table 2. Visual acuity at baseline and at last follow-up of the included studies

Author	Type of patients	Baseline BCVA (ETDRS)	Last BCVA (ETDRS)	p-value of BCVA change
Bilgic et al (REBA)	Treatment-naïve patients	49,4 ± 4,5	61,30 ± 3,80	0,011
Bilgic et al (PROBE)	Treatment-naïve patients	57,4 ± 4,5	65,30 ± 3,10	0,014
Tanaka et al	Treatment-naïve patients	62,5 ± 65,5	85,00	< 0,01
Bulirsch et al	Switch therapy patients	65,5 ± 71,0	85,00 ± 0,31	0,060
Abdin et al	Switch therapy patients	51 ± 16,0	50,00 ± 10,54	0,600
Haensli et al	Switch therapy patients	67,8 ± 7,2	72,20 ± 7,50	NA
Bilgic et al (REBA)	Switch therapy patients	40,0 ± 3,2	50,40 ± 4,80	0,014
Giunta et al	Switch therapy patients	57,7 ± 15,5	64.4 ± 15,90	<0.001
Coney et al	Switch therapy patients	60,8 ± 17,1	59,70 ± 3,7	0,420
Sharma et al	Switch therapy patients	64,0 ± 71,0	67,00 ± 70,50	0,330
Montesel et al	Switch therapy and treatment-naïve patients	65,0 ± 65,0	85,00 ± 0,60	0,778
Chakraborty et al	Switch therapy and treatment-naïve patients	45,00	85,00	<0.001
Enríquez et al	Switch therapy and treatment-naïve patients	64,1 ± 15,9	63,30 ± 17,20	0,650

BCVA: best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; NA: not available

There were two studies comprising treatment-naïve patients and one study reporting treatment-naïve patients separately. All three studies noted a statistically significant improvement in BCVA ($p < 0,05$). Two studies by Bilgic et al showed 7,8 letters gain (PROBE study) and 11,9 letters gain (REBA study) at last follow-up.

All studies that involved only switch therapy eyes or reported switch therapy eyes separately revealed improvement of BCVA by the end of follow-up; however, only two studies that describe this finding as statistically significant (Giunta et al and REBA study by Bilgic et al). Only one study by Abdin et al that reported visual acuity change at every visit, and it observed statistically significant visual gain by week 16 (p 0,001), but the visual acuity then remained constant throughout the rest of the study. In studies that reported combination of results for both treatment-naïve and switch therapy eyes, significant visual gain was only reported in one study ($p < 0,001$ by Chakraborty et al).

Table 3. Central retinal thickness at baseline and at last follow-up of the included studies

Author	Type of patients	Baseline CRT (μm)	Last CRT (μm)	p-value
Bilgic et al (REBA)	Treatment-naïve patients	428,1 ± 73,4	278,0 ± 47,2	0,0210
Bilgic et al (PROBE)	Treatment-naïve patients	398,1 ± 47,2	283,0 ± 57,2	0,0210
Tanaka et al	Treatment-naïve patients	399 ± 215	208	< 0,0001
Bulirsch et al	Switch therapy patients	409,43 ± 112,32	342,67 ± 99,05	<0,001
Abdin et al	Switch therapy patients	374 ± 158	298	0,0100
Haensli et al	Switch therapy patients	422,1 ± 97,3	353,6 ± 100,9	NA
Bilgic et al (REBA)	Switch therapy patients	483,2 ± 59,2	297,5 ± 53,4	0,0100
Giunta et al	Switch therapy patients	301,2 ± 65,5	264,8 ± 57,8	0,0002
Coney et al	Switch therapy patients	292,2 ± 113,3	257	< 0,0001
Sharma et al	Switch therapy patients	314 ± 94	263 ± 51	0,0027
Montesel et al	Switch therapy and treatment-naïve patients	470 ± 151	360 ± 144	0,0010
Chakraborty et al	Switch therapy and treatment-naïve patients	413,6 ± 64,6 μm	292,37 ± 13,5	<0,001
Enríquez et al	Switch therapy and treatment-naïve patients	296,7 ± 88,0	269,8 ± 66,5	0,0030

CRT: central retinal thickness; NA: not available

2. Anatomical marker

2.1. Central retinal thickness

One of the quantitative measurements of anatomical improvement was observed through changes in CRT (as shown in Table 3). At baseline, mean CRT was 384,74 µm and it was 289,82 µm at the last follow-up.

Three studies that assessed treatment-naïve eyes reported statistically significant changes in CRT from baseline to last follow-up (two studies by Bilgic et al and one by Tanaka et al). There were six studies that included only switch therapy eyes and one study that reported switch therapy eyes separately, all reported statistically significant changes in CRT from baseline to last follow-up, with mean change ranging from 35,2 µm (Coney et al) to 185,7 µm (Bilgic et al). A study by Abdin et al presented the change of CRT in every follow-up, and the improvement was statistically significant as early as week 4 (p 0,01), and it was fluctuating until it reached 28 weeks through the last follow-up (p 0,01). A study by Coney et al also presented data at different time points of the follow-up, and the CRT change was similar and all statistically significant at 12 months (reduced by 35,2 µm, $p < 0,0001$) and 18 months (reduced by 38,9 µm, $p < 0,0001$). All three studies that reported collective results for both treatment-naïve and switch therapy eyes observed statistically significant changes in CRT.

2.2. Subretinal fluid, intraretinal fluid, and pigment epithelial detachment

Quantitative improvement in the retina was also assessed through presence of IRF, SRF, and PED at baseline and at last follow-up (presented in Table 4). Retinal fluid was still considered present if it was stagnant or only partly regressed. Out of 12 studies, four did not report the data the final data of SRF, IRF, and PED; therefore, they were not included in the analysis.

There were three studies that did not include the statistical significance data on SRF and IRF reductions, but according to the rest of the studies, the reduction was statistically significant (study by Abdin et al, Giunta et a, Montesel et al, Chakraborty et al). Studies by Sharma et al and Bulirsch et al reported complete resolution of SRF in 39,4% and 57,3% of eyes, respectively. Seven studies reported a reduction in proportion of eyes with IRF, although only two studies showed the statistical significance (Giunta et al and Chakraborty et al). Studies by Sharma et al and Bulirsch et al reported complete resolution of IRF in 36,8% and 40,7% of eyes with IRF, respectively. There were five studies that reported the changes in PED, and statistical significance was observed in three studies by Tanaka et al, Abdin et al, and Chakraborty et al.

3. Injection interval

Out of 12 studies, only six studies reported the mean injection interval or interval between each injection. Extension of injection interval was observed in all studies that included only switch therapy patients (Haensli et al, Coney et al, and Giunta et al). The studies that reported the injection interval were summarized in Table 5. Haensli et al studied 12 eyes that had been previously treated with other anti-VEGF and brolucizumab was initiated within 6 weeks after prior injection, then continued a treat-and-extend protocol. It observed extension to 9.0 ± 2.8 weeks after switch to brolucizumab, compared to 5.3 ± 0.9 weeks before switch.[12] An analysis by Coney et

al divided the groups based on pre-switch intervals into < 8 weeks and ≥ 8 weeks, and reported that the group of eyes with pre-switch injection interval < 8 weeks experienced a longer injection up to 4,9 weeks after switching to brolucizumab at month 12 (p < 0,0001). A longer injection

Table 4. Retinal fluids at baseline and at last follow-up of the included studies

Author	Type of patients	Presence of SRF baseline (n eyes)	Presence of SRF in last follow up (n eyes)	Complete resolve of SRF (n eyes)	p-value	Presence of IRF baseline (n eyes)	Presence of IRF in last follow up (n eyes)	Complete resolve of IRF (n eyes)	p-value	Presence of PED baseline (n eyes)	Presence of PED in last follow up (n eyes)	Complete resolve of PED (n eyes)	p-value
Tanaka et al	Treatment-naïve patients	NA	NA	NA	NA	NA	NA	NA	NA	10	9 (8 regressed)	1	0,009
Bulirsch et al	Switch therapy patients	42	18	24	NA	27	16	11	NA	NA	NA	NA	NA
Abdin et al	Switch therapy patients	15	10	5	0,030	12	12	0	0,8	8	4	4	0,01
Haensli et al	Switch therapy patients	3	3 (2 regressed)	0	NA	4	4 (2 regressed)	0	NA	NA	NA	NA	NA
Giunta et al	Switch therapy patients	59	22	37	0,001	42	14	28	0,001	NA	NA	NA	NA
Sharma et al	Switch therapy patients	38	23 (17 regressed)	15	NA	19	12 (8 regressed)	7	NA	31	29 (13 regressed)	2	NA
Montesel et al	Switch therapy and treatment-naïve patients	17	3 (3 regressed)	14	0,011	12	3 (3 regressed)	9	0,065	16	14 (5 regressed)	2	0,811
Chakraborty et al	Switch therapy and treatment-naïve patients	64	18	46	0,001	67	43	NA	0,001	19	9	10	0,004

IRF: intraretinal fluid; NA: not available; PED: pigment epithelial detachment; SRF: subretinal fluid

interval to 1,5 weeks was also observed in the group of eyes with prior interval ≥ 8 weeks, although the result was not deemed statistically significant (p 0,13).

Table 8. Out of all 848 eyes included in this review, intraocular inflammation developed in 64 eyes (8,01%), while other adverse events occurred in 13 eyes (1,5%). Two studies by Bilgic et al (PROBE) and Sharma et al did not note any

Table 5. Injection interval of the included studies

Author	Type of patients	Injection protocol	Explanation of injection interval	p-value
Bilgic et al (REBA)	Treatment-naïve patients	Treat-and-extend	31,2% of eyes were extended to 12 weeks, 68,8% of eyes were maintained at 8 weeks	NA
Bilgic et al (PROBE)	Treatment-naïve patients	PRN	8 weeks	NA
Tanaka et al	Treatment-naïve patients	Treat-and-extend	4 weeks	NA
Haensli et al	Switch therapy patients	Treat-and-extend	The mean treatment interval was extended from 5,3 ± 0,9 weeks (before switch) to 9,0 ± 2,8 weeks.	NA
Coney et al	Switch therapy patients	PRN	Injection interval extended to 26,9 days (3.8 weeks)	<0,0001
Sharma et al	Switch therapy patients	Treat-and-extend	Patients who underwent more than one injection of brolucizumab received it at an interval of 4–6 weeks	NA
Giunta et al	Switch therapy patients	Treat-and-extend	Mean injection interval extended by 2,1 weeks from baseline (4,7 weeks) to last visit (6,8 weeks)	<0,001
Chakraborty et al	Switch therapy and treatment-naïve patients	PRN	The interval between 1st dose to 2nd dose: 10,98±3 weeks; 2nd dose to 3rd dose: 11,71±2,16 weeks; 3rd dose to 4th dose: 12,27±1,98 weeks; 4th dose to 5th dose: 11,69±2,07 weeks; 5th dose to 6th dose: 12 weeks	NA

NA: not available; PRN: pro re nata

4. Safety

For the safety outcome, we included both IOI and other adverse events unrelated to inflammation in this review, as reported on intraocular inflammation throughout the study. Table 7 shows the list of adverse events reported in all included studies. Almost all of the studies observed that the inflammation resolved, and

vision improved after topical corticosteroids (studies by Burlisch et al, Abdin et al, Montesel et al, Haensli et al, Tanaka et al, Enriquez et al). An exception was noted in a study by Chakraborty, in which it explained that the VA was already poor before the injection

Table 8. List of adverse events reported in all included studies

Adverse events	n (eyes)
IOI	
Anterior uveitis	7
Vitritis or intermediate uveitis	22
Anterior and intermediate uveitis	8
Retinal vasculitis and/or retinal vascular occlusion	9
Panuveitis	2
Posterior uveitis	1
IOI not specified	15
Total	64
Non-inflammation	
Ocular hypertension	2
Macular hole	1
Endophthalmitis	1
Subretinal hemorrhage and/or pigment epithelial tear	4
VH or opacities unrelated to inflammation	2
BRAO	1
Retinal detachment	1
PVD	1
Total	13

BRAO: branch retinal artery occlusion; IOI: intraocular inflammation, PVD: posterior vitreous detachment; VH: vitreous hemorrhage

DISCUSSION

This review describes the efficacy and safety of brolucizumab for nAMD in real clinical experience based on the published real-world data.

Statistically significant visual gain is observed in all studies (two studies by Bilgic et al and a study by Tanaka et al) that reported analysis for treatment-naïve eyes. The PROBE Study by Bilgic et al that focused on PRN injection of brolucizumab in treatment-naïve patients found a significant gain from 10 to 15 letters as early as 1 month after the first injection, while a study by Tanaka et al observed that BCVA improved to 4,5 letters ($p < 0,01$) after 3 monthly injections.[13,14] This finding is similar with the results from prior clinical trials of brolucizumab for treatment-naïve nAMD patients.[15] HAWK and HARRIER study, a phase-3, multicenter, randomized, double-masked clinical trial comparing 6 mg brolucizumab and aflibercept in treatment-naïve nAMD patients with treat-and-extend protocol, brolucizumab demonstrated noninferiority in visual gains from baseline to week 48 (+6,6 letters in HAWK and +6,9 letters in HARRIER, p value for noninferiority <0,001 for both results). [16] Similar findings of noninferiority were also noted in other randomized controlled trials comparing brolucizumab to aflibercept, namely studies by Mishra et al that used PRN protocol in treatment-naïve Indian patients and Matsumoto et al that applied treat-and-extend regimens in Japanese patients.[17,18]

In patients who had received prior anti-VEGF injections and then were switched to brolucizumab, visual gains were observed in the studies included in this review, but statistical significance was only observed in two studies (REBA study by Bilgic et al and Giunta et al). In three studies by Coney et al, Enriquez et al, and Abdin et al, a decrease of ETDRS letters on the final BCVA was observed. This was in line with previous study by Gupta et al that studied three monthly doses in recalcitrant nAMD patients previously treated with aflibercept, as it observed statistically significant reduction in central subfield thickness that did not translate to the visual gains in the patients.[2] The possible explanation is that most switch therapy patients had longstanding duration of disease, so that irreversible damage in the photoreceptors might have already happened due to combination of residual fluid, subretinal fibrosis, and retinal atrophy; therefore, visual recovery may be limited despite anatomical improvement.[2,19]

According to guidelines from the American Academy of Ophthalmology and European Society of Retinal Specialists, not only a decrease in visual acuity, but presence of retinal fluid also prompts retreatment with anti-VEGF in nAMD patients. [20] Despite the results of visual gain that varied between treatment-naïve and switch therapy patients, both groups observed significant improvement in CRT and reduction in retinal fluid after administration of brolucizumab. This favorable outcome in real-world OCT parameters was observed also in HAWK and HARRIER clinical trial, in which significant reductions of CST, IRF, and SRF were noted at week 16 of the study after 8 weeks of loading phase in all patients. [16] Retinal fluid accumulation is caused by elevated VEGF, that eventually results in edema and visual decrease, hence CRT and presence of retinal fluid are important indicators that can be recognized more quickly in active disease of nAMD.[16] This superior drying effect possessed by brolucizumab may be due to its lower molecular weight compared to other anti-VEGF that facilitates more effective penetration of the retina and choroid, resulting in increased distribution to the target site. [5]

Our study shows similar results as HAWK and HARRIER trials, in which the greatest effect of brolucizumab was observed on SRF, followed by IRF and PED. The presence of IRF at baseline has been linked to poorer visual acuity outcome in nAMD patients as shown in several previously published

clinical trials, such as CATT and HARBOR. [21,22] IRF may also return after a period of resolution, especially in eyes that show slower resolution at the initial stages. [23] A study by Saens-de-Viteri et al about administration of ranibizumab in nAMD patients described that presence of IRF was associated with development of fibrosis by the end of the study, thus resulting in worse visual outcome. [24] In patients whose IRF did not resolve until after 12 weeks, earlier follow-up and re-treatment may be considered.[23] In our review, significant resolution or regression of SRF were observed in many studies. Resolution of SRF also plays a role in improvement of vision.[21] However, in contrast to IRF, patients with residual SRF may still have good functional outcomes. FLUID study tolerated SRF to some extent, except at the fovea, where amount higher than 200 µm requires re-treatment.[18] It showed that a group of patients with a tolerable degree of SRF achieved BCVA that was noninferior to those with completely resolved SRF by the end of the 24-month study.[18] This tolerance results in an extended injection interval, with relatively equal functional outcomes and less adverse events. According to CATT and HARBOR trials, residual SRF at the end of the study was associated with better visual acuity, as SRF is thought to contain beneficial growth factors that can protect against macular atrophy in eyes with inactive CNV.[21,26] Studies with longer duration that explore the association between the presence of retinal fluids with retinal anatomy and functional outcomes at different timeframe are warranted.

Brolucizumab also showed effect on PED. PED is described as a separation of RPE from Bruch's membrane because of the presence of sub-RPE fluid, blood, fibrovascular membrane, or drusenoid material.[3] Based on the results of HAWK and HARRIER, the percentage of patients treated with brolucizumab who had sub-RPE fluid was much lower, in comparison to patients treated with aflibercept.[16] In CATT, although sub-RPE fluid was reduced by the end of the study, it did not correlate to final BCVA.[20] PED caused by sub-RPE fluid may not have significant association to functional outcomes as it does not always hamper the interactions between photoreceptors and RPE.[20] Unfortunately, the studies included in the review did not mention the etiology of PED, except one study by Chakraborty et al, in which it only included fibrovascular PED. Fibrovascular PED is often associated with poorer visual outcome, non-responsiveness to therapy, and higher incidence of RPE tears and re-activation.[20,21] As anti-VEGF therapy mainly works by reducing vascular permeability and exudation, the impact on fibrovascular tissue is likely to be suboptimal.[20] Although decision to treat nAMD is not usually based on PED, studies that further evaluate etiology and quantitative morphology of PED and their association to visual acuity are needed.

Brolucizumab also provides prolonged duration of action as seen in extended interval of injections, both in clinical trials and real-world studies. In this review, all studies reported extension of injection interval in switch therapy patients (Haensli et al, Coney et al, and Giunta et al). In treatment-naïve patients, dosing can be scheduled with 12-week interval as reported in a clinical trial by Mishra et al, as well as in a proportion of patients in real clinical setting according to Bilgic et al.[13,17] A study by Giunta et al that also studied switch therapy patients noted an extension of injection interval to 2,1 weeks. It also analysed the correlation between injection interval and BCVA or CRT, in which no correlation was found (p 0,39). Most of the patients who were switched to brolucizumab had persistent fluid or inability to extend treatment interval, hence the use of brolucizumab may prolong treatment interval, reduce patients' visits, and alleviate treatment burden associated with nAMD.[22]

Despite the advantages offered by brolucizumab, inflammatory events following brolucizumab injection have been reported. There

are various clinical features of brolucizumab-associated IOI, ranging from anterior inflammation, such as presence of anterior chamber cells, conjunctival injection, keratic precipitates, Descemet fold, corneal edema, to posterior findings namely vitreous cells or opacities, sheathing or occlusion in retinal arteries, retinal ischemia, changes in retinal veins, and optic nerve swelling.[23] The postulated mechanism of IOI after brolucizumab heavily relies on hypersensitivity. As anti-VEGF molecules are proteins with potentials to be immunogenic, it is proposed that brolucizumab molecules trigger deposition of immune complexes that cause occlusion in the blood vessel walls.[22]

In our review, only two studies by Bilgic et al and Sharma et al that did not find any cases of IOI. This might be possible in the later study due to its short follow-up time (7,2 weeks). However, other studies with similar follow-up time observed IOI, and other studies also observed that signs of inflammation appeared as early as 3 days after the injection.[19,24] IOI was observed in 64 eyes (8,01%). This percentage is higher if compared to the numbers of IOI observed in post hoc review of HAWK and HARRIER, which noted 4,6% IOI (50 eyes out of 1088 enrolled eyes).[9,25] Most of the reported IOI cases were intermediate uveitis or vitritis (34,3% out of all reported IOIs), while retinal vasculitis and/or retinal vascular occlusion came in second (14,06%); with most patients mostly presented with decrease in visual acuity.

The severity varied between studies, from only mild inflammation that resolved with corticosteroid eyedrops, to severe form that needed systemic corticosteroids or more invasive procedures, such as intravenous administration of methylprednisolone (1 eye with RV and RVO in a study by Haensli et al), subtenon injection of triamcinolone acetonide (studies by Tanaka et al and Enriquez et al), subconjunctival injection of dexamethasone (4 eyes in a study by Burlisch et al), and vitrectomy and intraoperative triamcinolone (1 eye in a study by Enriquez at al). Inflammation was observed as early as 3 days after injection, to 6 months at the latest. IOI was mostly observed on patients who were switched to brolucizumab, compared to treatment-naïve patients, indicating the possibility that previous anti-VEGF is one of the risk factors of developing IOI in patients who received brolucizumab. One hypothesis in a study by Sharma et al stated that patients who received previous anti-VEGF injections, such as aflibercept or ranibizumab, have more anti-drug antibodies that may induce inflammation; however, further studies are warranted.[26]

In studies that reported the outcome after treatment, inflammation mostly cleared up and vision recovered without clinically relevant deterioration in overall VA, except in a study by Chakraborty et al in which the patients were already with poor vision before the injection.[27] Other than inflammatory events, other adverse events were also noted, such as subretinal hemorrhage and pigment epithelial tear and ocular hypertension. A case endophthalmitis was reported in a study by Enriquez et al; however, it was proposed to be injection-related, rather than due to inflammation reaction, because the patient responded well to administration of intravitreal vancomycin.[28]

Limitation and strengths

This review is not without limitations. The variability between follow-up time may affect the heterogeneity of the results. A few included studies also presented incomplete data, such as statistical significance, thus creating difficulty during the review of the literature. As this paper was being written, there has not been any consensus on which

tool to use to assess real-world evidence. The strengths of this study were in the involvement of patients from various countries, as well as enough efficacy parameters to be objectively analyzed, such as BCVA and CRT. We also further evaluated the effect of brolucizumab on IRF, SRF, and PED.

CONCLUSION

In conclusion, this review of real-world data demonstrates the efficacy of brolucizumab in treatment-naïve and patients who were switched to brolucizumab in real clinical setting. Although the improvement in visual acuity was mostly observed in treatment-naïve patients, statistically significant reductions in retinal thickness and retinal fluids, as well as extended interval of injections, were noted in both groups of patients. These findings denote the ability of brolucizumab to bring down disease activity, as also observed in previous clinical trials, that eventually lessens treatment burden in nAMD patients. Further long-term, real-world studies are required to evaluate the effect of brolucizumab on SRF, IRF, and PED and their implications on disease activity criteria and treatment strategies. Clinicians must be aware of possible inflammatory events that may ensue after the injection. Pre-injection documentation and post-injection examination may aid timely identification and prompt treatment should adverse events arise, thus minimizing further vision impairment.

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