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Review

RETINAL VASCULITIS OR VASCULAR OCCLUSION AFTER BROLUCIZUMAB FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

A Systematic Review of Real-World Evidence

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Purpose: Retinal vasculitis or vascular occlusion (RV/RO) have been reported after brolucizumab for neovascular age-related macular degeneration. This systematic literature review evaluated RV/RO events after brolucizumab in real-world practice.

Methods: Systematic literature searches identified 89 publications; 19 were included.

Results: Publications described 63 patients (70 eyes) with an RV/RO event following brolucizumab. Mean age was 77.6 years and 77.8% of patients were women; 32 eyes (45.7%) received one brolucizumab injection before RV/RO. Mean (range) time to event from last brolucizumab injection was 19.4 (0–63) days, with 87.5% of events occurring within 30 days. Among eyes with preevent and postevent visual acuity (VA) assessments, 22/42 eyes (52.4%) showed unchanged (±0.08 logMAR) or improved vision from last recorded preevent assessment at latest follow-up, whereas 15/42 eyes (35.7%) showed ≥0.30 logMAR (≥15 letters) VA reduction. Patients with no VA loss were on average slightly younger and had a higher proportion of nonocclusive events.

Conclusion: Most RV/RO events reported after brolucizumab in early real-world practice occurred in women. Among eyes with VA measurements, approximately half experienced VA loss; overall, about one-third had VA reduction of ≥0.30 logMAR at latest follow-up, with indications of regional variations.

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Age-related macular degeneration (AMD) is a leading cause of permanent visual impairment and blindness, and late-stage neovascular (wet) AMD (nAMD) is associated with most severe vision loss cases.[1] Anti-vascular endothelial growth factor (VEGF) agents are the first-line treatment for nAMD.[1] Brolucizumab is a humanized monoclonal antibody single-chain variable fragment, and its low molecular weight allows brolucizumab to be administered at higher molar concentrations than previous anti-VEGF treatments.[2] In the phase 3 HAWK and HARRIER studies, brolucizumab was noninferior to aflibercept for best-corrected visual acuity at week 48, and demonstrated superiority to aflibercept for anatomical outcomes.[3] At weeks 48 and 92, approximately 50% and 40–45%, respectively, of brolucizumab-treated patients were maintained with a dosing interval of every 12 weeks, with no reduction in efficacy compared with the fixed aflibercept regimen of dosing every 8 weeks.[3,4] However, monthly injections with brolucizumab are not recommended beyond the initial three loading doses[5,6]; in the phase 3 MERLIN study, brolucizumab was associated with an increased incidence of intraocular inflammation (IOI) compared

with aflibercept when dosed every 4 weeks after the loading phase.[7]

Since the approval of brolucizumab for nAMD by the U.S. Food and Drug Administration in October 2019, there have been reports of numerous cases of IOI, including retinal vasculitis (RV) and retinal vascular occlusion (RO), after brolucizumab injections.[8] In response, Novartis initiated a partnership with an external safety review committee (SRC) to better understand the adverse events emerging from brolucizumab use. A review of postmarketing safety case reports in conjunction with the SRC concluded that there was a confirmed safety signal of adverse events of RV and/or RO, typically in the presence of IOI, with brolucizumab that could result in severe vision loss.[9,10]

The incidence of RV and/or RO after brolucizumab treatment for nAMD has been evaluated in real-world practice. A retrospective cohort study using two large

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U.S. health care databases showed an overall incidence of 0.6% for RV and/or RO.[11] In postmarketing surveillance data, the rate of RV and/or RO events with brolucizumab in patients with nAMD was 15.5 per 10,000 injections worldwide (from October 2019 to November 2021).[12]

In the current systematic literature review, searches focused on identifying reports of adverse events of RV and/or RO (with or without IOI) after the use of brolucizumab for nAMD in real-world clinical practice. The aim was to gain a better understanding of the nature and characteristics of these events, how they develop over time, and how patients respond to treatments for them.

Methods

Systematic literature searches were conducted to identify publications reporting an adverse event of RV and/or RO after brolucizumab injection for nAMD in real-world clinical practice and published between January 1, 2019 and June 30, 2021 for inclusion in the review (see the **Supplemental Digital Content, Methods and Tables S1–S3** http://links.lww.com/WNL/C688 for details of the search strategy, screening, and data extraction and analysis). In addition, an email request was sent to the corresponding author of each selected publication for additional information about each eye with an RV and/or RO event reported in their publication (see **Supplemental Digital Content, Methods and Table S4** http://links.lww.com/WNL/C688).

Results

Publication Details

The literature searches identified a total of 89 publications from the Embase and MEDLINE databases, of which 19 met the criteria for inclusion in the review (**Supplemental Digital Content, Figure S1**, http://links.lww.com/WNL/C688).[8,13–30] Together, these publications described cases from five countries: the United States (7 publications), Germany (6 publications), Japan (4 publications), and Canada and India (1 publication each).

In total, these publications reported on 63 individual patients with RV and/or RO as an adverse event after brolucizumab injection, affecting 70 eyes (Table 1). There were 41 patients from the United States (46 affected eyes), 14 from Japan (14 eyes), six from Germany (8 eyes), and one each from Canada (1 eye) and India (1 eye). Most publications (n = 13) included one patient with an RV/RO event, and four publications each reported findings for two to five individuals. Two publications, both from the United States, presented information for more than 10 patients: one reported on 12 patients (15 eyes),[15] and the other on 25 patients (26 eyes) with individual patient information provided for four events.[8] Most of the publications presented individual case reports or case series; four publications reported findings from observational studies evaluating consecutive patients treated with brolucizumab.[16,17,27,28]

Authors from 10 of the 19 publications (52.6%) responded to the request for additional data, providing information on 20 patients (22 eyes). Most of these cases were from Japan (14 patients/14 eyes), with all of the Japanese authors responding to the request (see the Acknowledgments for details).

Patient Characteristics and Event Details

Patient characteristics and event details are summarized in Table 1; details for individual patients/eyes are shown in **Supplemental Digital Content, Tables S5 and S6** http://links.lww.com/WNL/C688. Overall, the mean age was 77.6 years (range, 52–94 years) and 77.8% of patients were women, with this proportion being greater among patients from North America (90.5%) than those from Germany (66.7%) and Japan (42.9%). Hypertension (56.5% of patients), autoimmune/inflammatory disorders (39.1%), and hyperlipidemia (30.4%) were the most commonly reported concomitant systemic diseases. In total, seven patients (11.1%) experienced bilateral events: five patients in North America and two in Germany. All except two of the events (97.1%) had concurrent IOI. Occlusive RV accounted for 78.6% of events, with this proportion being lower in Japan (50.0%) than in North America (87.2%) and Germany (87.5%).

Eyes had received a mean of 1.7 brolucizumab injections before the event (median, two; range, 1–3). Overall, 32 eyes (45.7%), 27 eyes (38.6%), and 11 eyes (15.7%) were treated with one, two, and three previous brolucizumab injections, respectively. In North America and Japan, 48.9% and 50.0% of eyes, respectively, received one brolucizumab injection before the event; in Germany, most eyes (87.5%) had two brolucizumab injections before the event. None of the patients received an additional brolucizumab injection in the same or contralateral eye after the reported RV and/or RO event.

The mean time from the last brolucizumab injection to the onset of event symptoms (time to event) was 19.4 days (median, 17 days; range, 0–63 days; **Supplemental Digital Content, Figure S2a**, http://links.lww.com/WNL/C688); this interval was similar for cases from

Table 1. Patient Characteristics and Medical History, Event Details, and Previous Anti-VEGF Treatment

	North America	Germany	Japan	All Cases*
Number of patients (eyes)	42 (47)	6 (8)	14 (14)	63 (70)
Age, years	n = 15†	n = 6†	n = 14†	n = 36†
Mean (SD)	79.3 (7.8)	76.0 (6.0)	77.6 (10.5)	77.6 (8.9)
Sex, n (% of patients)	n = 42†	n = 6†	n = 14†	n = 63†
Male	4 (9.5%)	2 (33.3%)	8 (57.1%)	14 (22.2%)
Female	38 (90.5%)	4 (66.7%)	6 (42.9%)	49 (77.8%)
Event eye, n (% of patients)	n = 42†	n = 6†	n = 14†	n = 63†
Unilateral	37 (88.1%)	4 (66.7%)	14 (100%)	56 (88.9%)
Bilateral	5 (11.9%)	2 (33.3%)	0	7 (11.1%)
Event type, n (% of eyes)	n = 47‡	n = 8‡	n = 14‡	n = 70‡
Occlusive RV	41 (87.2%)	7 (87.5%)	7 (50.0%)	55 (78.6%)
Nonocclusive RV	6 (12.8%)	1 (12.5%)	7 (50.0%)	15 (21.4%)
Number of brolucizumab injections (per eye) before event	n = 47‡	n = 8‡	n = 14‡	n = 70‡
Mean (SD)	1.68 (0.75)	1.88 (0.35)	1.71 (0.83)	1.70 (0.73)
Time from last brolucizumab injection to event, days§	n = 25‡	n = 8‡	n = 14‡	n = 48‡
Mean (SD)	22.6 (14.6)	7.9 (8.7)	21.6 (8.6)	19.4 (13.3)
Time from first brolucizumab injection to event, days§	n = 18‡	n = 6‡	n = 14‡	n = 39‡
Mean (SD)	32.4 (28.3)	36.2 (20.6)	50.1 (41.8)	38.5 (33.4)
Other previous anti-VEGF injections¶, number of treated eyes (%)	n = 46‡	n = 8‡	n = 14‡	n = 69‡
Any previous anti-VEGF¶	46 (100%)	8 (100%)	7 (50.0%)	62 (89.9%)
No previous anti-VEGF¶	0	0	7 (50.0%)	7 (10.1%)
Number of previous anti-VEGF injections (excluding treatment-naive eyes)¶	n = 14‡	n = 4‡	n = 4‡	n = 23‡
Mean (SD)**	34.1 (24.4)	27.0 (22.1)	37.5 (12.5)	33.2 (21.2)
Type of previous treatment, n (% of eyes)††	n = 24‡	n = 8‡	n = 14‡	n = 47‡
Aflibercept	20 (83.3%)	4 (50.0%)	3 (21.4%)	28 (59.6%)
Bevacizumab	11 (45.8%)	0	0	12 (25.5%)
Ranibizumab	9 (37.5%)	2 (25.0%)	3 (21.4%)	15 (31.9%)
Not specified	0	3 (37.5%)	3 (21.4%)	6 (12.8%)
None	0	0	7 (50.0%)	7 (14.9%)
Ocular procedures, n (% of eyes)	n = 21‡	n = 0‡	n = 5‡	n = 27‡
Cataract extraction	4 (19.0%)	—	0	5 (18.5%)
Retinal laser	0	—	1 (20.0%)	2 (7.4%)
Concomitant systemic disease, n (% of patients)	n = 17†	n = 0†	n = 5†	n = 23†
CVD/hypertension	12 (70.6%)	—	3 (60.0%)	15 (65.2%)
Hypertension	10 (58.8%)	—	3 (60.0%)	13 (56.5%)
Hyperlipidemia	6 (35.3%)	—	1 (20.0%)	7 (30.4%)
Diabetes	3 (17.6%)	—	0	3 (13.0%)
Autoimmune/inflammatory	9 (52.9%)	—	0	9 (39.1%)
Arthritis	4 (23.5%)	—	0	4 (17.4%)
Hypothyroid	4 (23.5%)	—	0	4 (17.4%)
Cancer	4 (23.5%)	—	0	4 (17.4%)

*Includes patients/eyes from all countries, including India (1 patient/1 eye).
†Number of patients with available data.
‡Number of eyes with available data.
§Time to occurrence of symptoms and/or signs of IOI and/or RV on examination.
¶Excluding brolucizumab.
**Only includes pretreated eyes for which an exact number of injections was reported.
††Eyes could receive more than one type of treatment.
CVD, cardiovascular disease; IOI, intraocular inflammation; RV, retinal vasculitis; SD, standard deviation; VEGF, vascular endothelial growth factor.

North America and Japan, but seemed shorter for cases from Germany (7.9 days). Most events (87.5%) occurred in the 30 days after the last brolucizumab injection, with six eyes (12.5%) experiencing an event more than 30 days after the last injection. The mean time to event from last injection was similar for eyes with one previous brolucizumab injection compared with those with more than one previous injection (19.9 days and 18.8 days, respectively). The mean time from the first brolucizumab injection to the event was 38.5 days for 39 eyes with available data (median, 28 days; range, 0–161 days; **Supplemental Digital Content, Figure S2b**, http://links.lww.com/WNL/C688); this interval seemed to be shorter for North American cases (32.4 days) and longer for Japanese cases (50.1 days). Overall, 89.9% of eyes had received previous treatment with at least one other anti-VEGF agent besides brolucizumab. All seven eyes with no other previous anti-VEGF treatment were reported in Japan, with events observed after one and more than one previous brolucizumab injection in two and five eyes, respectively.

The range of imaging techniques used in the diagnosis of RV/RO events varied across the cases included in the review, with the use of fluorescein angiography (FA) reported in about 70% of cases (see **Supplemental Digital Content, Table S7,** http://links.lww.com/WNL/C688 for individual eye data). In eyes with available FA imaging data, filling defects were reported in 70.4% of cases and were more frequently reported for arterial than venous vessels (59.3% and 33.3% of cases, respectively). However, it is important to note that the reporting of FA findings and the timing of FA relative to the event and its treatment varied across the publications.

Visual Acuity

Visual acuity data, presented as logarithm of the minimal angle of resolution (logMAR) values together with Snellen equivalents, are summarized in Table 2 (see **Supplemental Digital Content, Table S8** http://links.lww.com/WNL/C688 for individual eye data). At the last recorded assessment before the event, mean visual acuity was 0.44 (median, 0.30; range, −0.18–1.90) among the 46 eyes with available data. The latest recorded mean visual acuity during follow-up was 0.81 (median, 0.40; range, −0.18–2.70) and was measured at a mean of 94.3 days (median, 51 days; range, 4–210 days) after the event. There were, however, apparent differences in visual acuity across the regional subgroups (Table 2). Mean preevent visual acuity was higher in eyes from Japanese publications (0.28; median, 0.22; range, −0.18–1.22) than in those from North America (0.46; median, 0.40; range, 0.10–1.90) or Germany (0.60; median, 0.40; range, 0.20–1.30), as was the latest postevent mean visual acuity score (mean/median [range]: Japan, 0.22/0.15 [–0.18–1.00]; North America, 1.12/0.80 [0.10–2.70]; Germany, 0.93/0.40 [0.30–2.70]). The latest postevent visual acuity was recorded at a mean follow-up of 148.7, 49.9, and 137.2 days for cases from Japan, North America, and Germany, respectively. Mean postevent visual acuity was similar to the preevent levels in Japanese cases, but was below preevent levels in those from the other regional subgroups.

Overall, there were 42 eyes for which preevent and postevent visual acuity data were available; among these, 22 eyes (52.4%) were reported to have no loss of visual acuity at the latest assessment after the event, with visual acuity unchanged (±0.08 logMAR [±4 Early Treatment Diabetic Retinopathy Study [ETDRS] letters]) or improved from the last recorded preevent assessment (Figure 1). In comparison, 20 eyes (47.6%) were reported to have reduced vision after the event (loss of visual acuity of ≥0.10 logMAR [≥5 ETDRS letters] from preevent level). For 15 eyes (35.7%), visual acuity decreased by at least 0.30 logMAR (15 ETDRS letters) from the last recorded preevent score to the latest postevent follow-up assessment; this reduction was reported in seven of 22 eyes (31.8%) with one brolucizumab injection and in eight of 20 eyes (40.0%) with more than one brolucizumab injection.

Publications from Japan reported that 12 eyes (85.7%) experienced no reduction in vision after the event. This compares with eight eyes (36.4%) and two eyes (40.0%) reported in North American and German publications, respectively. Visual acuity decreased by at least 0.30 logMAR in 12 eyes (54.5%) and three eyes (60.0%) from North American and German publications, respectively, but in none of the eyes from Japanese publications. Among the eyes with available preevent and postevent visual acuity data, no loss of visual acuity at the event was reported for 14 eyes (of 41 with event data; 34.1%), of which eight were from Japan and six were from North America; conversely, 27 eyes (65.9%) were reported to have reduced vision at the event compared with the last preevent assessment (North America, 16 eyes; Japan, six eyes; Germany, four eyes; and India, one eye). **Supplemental Digital Content, Figure S3**, http://links.lww.com/WNL/C688 shows changes in visual acuity over time for individual eyes with available preevent and postevent visual acuity data and timelines.

Treatment for RV/RO Events

There were 47 eyes (67.1%) with available treatment information. Among these, 42 eyes (89.4%) were treated with topical corticosteroids (CS) after the event

Table 2. Visual Acuity

	North America	Germany	Japan	All Cases*
Visual acuity, logMAR				
Preevent†	n = 25‡	n = 6‡	n = 14‡	n = 46‡
Mean (SD)	0.46 (0.35)	0.60 (0.44)	0.28 (0.32)	0.44 (0.37)
Median (range)	0.40 (0.10–1.90)	0.40 (0.20–1.30)	0.22 (−0.18–1.22)	0.30 (−0.18–1.90)
At event	n = 25‡	n = 7‡	n = 14‡	n = 47‡
Mean (SD)	1.15 (0.84)	1.47 (0.62)	0.42 (0.45)	1.01 (0.81)
Median (range)	1.00 (0.10–2.70)	1.30 (0.70–2.70)	0.22 (−0.08–1.30)	0.70 (−0.08–2.70)
Postevent (latest recorded)	n = 22‡	n = 7‡	n = 14‡	n = 44‡
Mean (SD)	1.12 (0.87)	0.93 (0.90)	0.22 (0.33)	0.81 (0.83)
Median (range)	0.80 (0.10–2.70)	0.40 (0.30–2.70)	0.15 (−0.18–1.00)	0.40 (−0.18–2.70)
Visual acuity, Snellen equivalents				
Preevent†	n = 25‡	n = 6‡	n = 14‡	n = 46‡
Mean	20/58	20/80	20/38	20/55
Median (range)	20/50 (20/25 to CF)	20/50 (20/32 to 20/400)	20/33 (20/13 to 20/333)	20/40 (20/13 to CF)
At event	n = 25‡	n = 7‡	n = 14‡	n = 47‡
Mean	20/283	20/590	20/53	20/205
Median (range)	20/200 (20/25 to LP)	20/400 (20/100 to LP)	20/33 (20/17 to 20/400)	20/100 (20/17 to LP)
Postevent (latest recorded)	n = 22‡	n = 7‡	n = 14‡	n = 44‡
Mean	20/264	20/170	20/33	20/129
Median (range)	20/125 (20/25 to LP)	20/50 (20/40 to LP)	20/29 (20/13 to 20/200)	20/50 (20/13 to LP)
Time from event, days				
Preevent VA assessment	n = 9‡	n = 4‡	n = 14‡	n = 28‡
Mean (SD)	−26.6 (15.8)	−16.0 (19.6)	−22.4 (7.8)	−22.0 (13.2)
Median (range)	−23 (−7 to −63)	−8.5 (−2 to −45)	−24.5 (−11 to −35)	−21 (−1 to −63)
Postevent VA assessment	n = 22‡	n = 5‡	n = 13‡	n = 41‡
Mean (SD)	49.9 (57.6)	137.2 (75.1)	148.7 (62.6)	94.3 (76.4)
Median (range)	28 (7–191)	174 (4–180)	168 (42–210)	51 (4–210)
Postevent VA versus *preevent VA, n (%)*§	n = 22‡	n = 5‡	n = 14‡	n = 42‡
Improved/unchanged¶	8 (36.4%)	2 (40.0%)	12 (85.7%)	22 (52.4%)
Reduced**	14 (63.6%)	3 (60.0%)	2 (14.3%)	20 (47.6%)

*Includes patients/eyes from all countries, including India (1 patient/1 eye).
†Last recorded VA before event.
‡Number of eyes with available data.
§VA at latest recorded postevent assessment compared with the last preevent VA.
¶Improved: defined as a decrease of ≥0.10 logMAR (increase of ≥5 ETDRS letters) from the last preevent VA score. Unchanged: defined as a change of ±0.00–0.08 logMAR (±0–4 ETDRS letters) from the last preevent VA score.
**Reduced: defined as an increase of ≥0.10 logMAR (decrease of ≥5 ETDRS letters) from the last preevent VA score.
CF, count fingers; ETDRS, Early Treatment Diabetic Retinopathy Study; logMAR, logarithm of the minimal angle of resolution; LP, light perception; SD, standard deviation; VA, visual acuity.

(Table 3 and **Supplemental Digital Content, Table S5,** http://links.lww.com/WNL/C688). Overall, 25 eyes (53.2%) received an ocular CS injection, with this treatment approach being more frequently used in Japan (100% of eyes) and Germany (62.5%) than in North America (25.0%). In Japan, all 14 eyes received a sub-Tenon triamcinolone acetonide injection; in North America and Germany, ocular CS treatments included intravitreal dexamethasone implants (five eyes) and intravitreal dexamethasone injections (two eyes). Six eyes (10.6%) underwent pars plana vitrectomy (North America, three eyes; Germany, two eyes; India, one eye) after the event. Approximately half of patients (22/41; 53.7%) received systemic CS therapy, with this approach being more common in Germany (100%) and North America (65.0%) than in Japan (21.4%). Overall, oral CS treatment was more widely used than intravenous CS therapy (20 and four patients, respectively).

Subgroups According to Visual Acuity Outcome

Key patient characteristics and types of postevent treatment were tabulated to assess potential differences between cases with no loss of vision and those with reduced visual acuity after the event (Table 4). Cases with no vision loss seemed to be slightly younger

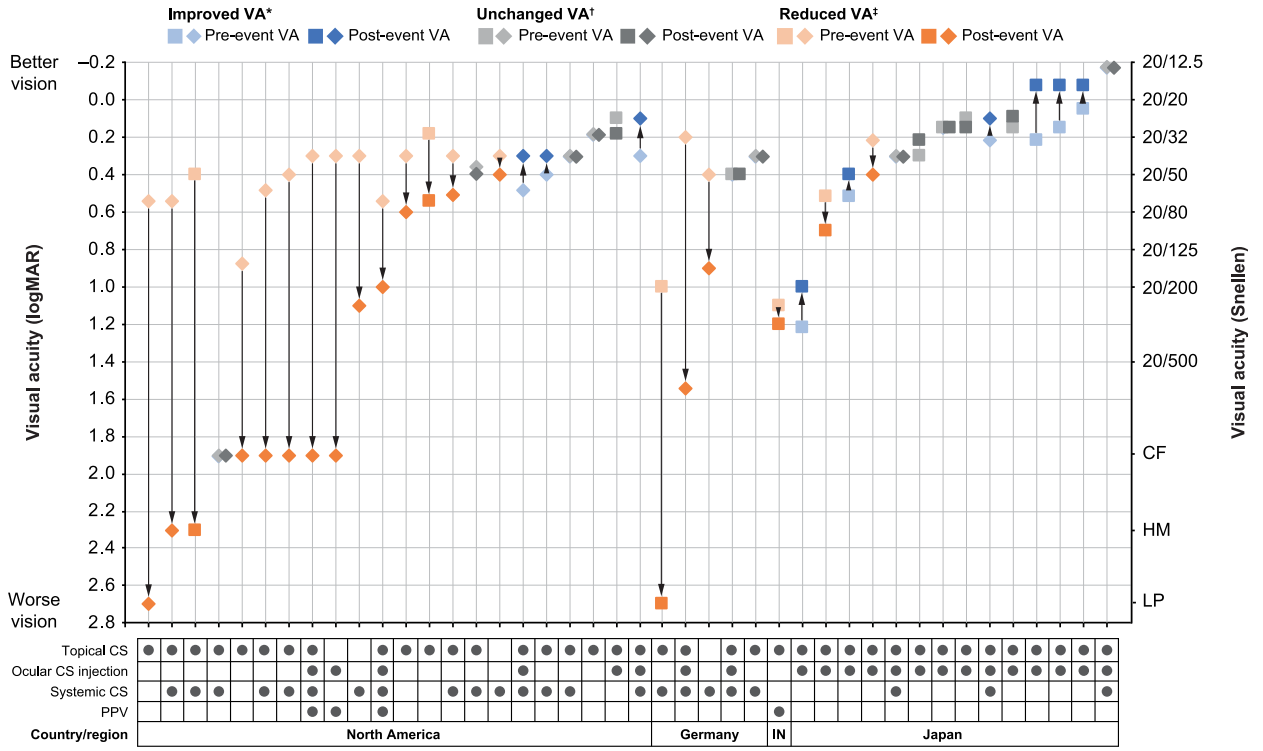

Fig. 1. Preevent and postevent VA data for the 42 individual eyes that had VA values preevent and postevent. Graph shows the last preevent VA value and the latest postevent VA value for eyes with available preevent and postevent VA data. Squares (■) indicate eyes with >20 weeks of follow-up after the event; diamonds (♦) indicate eyes with ≤20 weeks of follow-up after the event. Adverse event treatment for each eye is shown below the graph (●), together with the country/region. *Improved VA: decrease of ≥0.10 logMAR (increase of ≥5 ETDRS letters) from the last preevent VA score at the latest postevent assessment. †Unchanged VA: change of ±0.00–0.08 logMAR (±0–4 ETDRS letters) from the last preevent VA score at the latest postevent assessment. ‡Reduced VA: increase of ≥0.10 logMAR (decrease of ≥5 ETDRS letters) from the last preevent VA score at the latest postevent assessment. CF, count fingers; CS, corticosteroid; ETDRS, Early Treatment Diabetic Retinopathy Study; HM, hand movement; IN, India; logMAR, logarithm of the minimal angle of resolution; LP, light perception; PPV, pars plana vitrectomy; VA, visual acuity.

(mean: 75.9 years vs. 79.7 years) and had a higher proportion of nonocclusive events (45.5% vs. 5.0%) than those with reduced vision. Mean time to event from the last brolucizumab injection was longer for eyes with no vision loss than those with loss of visual acuity. Mean visual acuity at the event was worse for eyes with reduced vision at latest postevent assessment than for eyes with no loss of vision postevent, whereas mean visual acuity at the last preevent assessment was similar in the two groups. The mean decrease in visual acuity from the last preevent measurement to the event was smaller for cases with no loss of vision (0.12 logMAR [approximately equivalent to six ETDRS letters or 1.2 lines of visual acuity]) than for cases with reduced vision (0.94 logMAR [approximately equivalent to 47 ETDRS letters or 9.4 lines of visual acuity]). The proportion of cases treated with systemic CS was similar in the two groups.

Analysis of cases from North America also suggested that patients with no loss of vision were on average younger (74.0 years vs. 82.7 years) and had a longer time from the last brolucizumab injection to the event than those with reduced postevent vision, although the number of cases was limited. Evaluation of cases with no vision loss showed several differences between cases from Japan and those from Germany and North America. These included slightly higher patient age, higher proportions of men and nonocclusive events, and better mean preevent visual acuity in Japanese than in non-Japanese cases; however, mean changes in visual acuity at the event from the preevent assessment were similar in cases with no vision loss from Japanese and non-Japanese publications, as were mean changes in visual acuity from the preevent assessment to the latest postevent measure. The use of ocular CS injections and systemic CS also differed between the groups, with ocular CS injections being common in Japanese eyes with no vision loss (reflecting use in all reported Japanese cases), and systemic CS use being widespread in non-Japanese cases with no loss of vision.

Discussion

This systematic literature review summarizes the information from 63 patients with RV and/or RO

Table 3. Treatment for the RV/RO Event

	North America	Germany	Japan	All Cases*
Treated eyes, n (%)†	n = 24‡	n = 8‡	n = 14‡	n = 47‡
Topical CS	20 (83.3%)	8 (100%)	14 (100%)	42 (89.4%)
Ocular CS injection	6 (25.0%)	5 (62.5%)	14 (100%)	25 (53.2%)
STTA	1 (4.2%)	0	14 (100%)	15 (31.9%)
Dexamethasone	4 (16.7%)	5 (62.5%)	0	9 (19.1%)
Pars plana vitrectomy	3 (12.5%)	2 (25.0%)	0	6 (12.8%)
Treated patients, n (%)	n = 20§	n = 6§	n = 14§	n = 41§
Systemic CS	13 (65.0%)	6 (100%)	3 (21.4%)	22 (53.7%)
Oral¶	12 (60.0%)	5 (83.3%)	3 (21.4%)	20 (48.8%)
Intravenous¶	2 (10.0%)	2 (33.3%)	0	4 (9.8%)

*Includes patients/eyes from all countries, including India (1 patient/1 eye).
†Eyes could receive more than one type of treatment.
‡Number of eyes with available data.
§Number of patients with available data.
¶Patients could receive both oral and intravenous treatment.
CS, corticosteroid; RV, retinal vasculitis; RO, retinal vascular occlusion; STTA, sub-Tenon triamcinolone acetonide.

(affecting 70 eyes) after brolucizumab treatment for nAMD in real-world clinical practice. Most events included in this review were reported as case series or individual case reports. The results may therefore not be directly comparable with findings from real-world studies in which the cases are sampled in a consecutive fashion and patient characteristics are reported in a structured manner.

In the current review, most patients (almost 80%) were women. Approximately 46% of eyes had received one brolucizumab injection before the event, with the remaining eyes receiving two or three previous brolucizumab injections, indicating that the publications reflect earlier clinical experiences with brolucizumab and do not assess the risks associated with a greater number of injections. Overall, the mean time to the event was less than 20 days after the last injection. This time may have been affected by the visit schedule used by physicians because some events may have been observed at routine follow-up. Among eyes with recorded visual assessments, approximately one-third of eyes experienced no loss of visual acuity at the event and almost 53% of eyes experienced no loss of visual acuity at the latest recorded follow-up after the event. Approximately one-third of eyes had a reduction in visual acuity of at least 0.30 logMAR (15 ETDRS letters) at latest follow-up compared with preevent levels. However, regional differences were observed in visual acuity. Japanese publications reported higher preevent mean visual acuity in affected eyes than in North American or German cases. The proportion of eyes with no loss of visual acuity at latest follow-up was higher among Japanese cases (85.7%) than those from North America (36.4%) or Germany (40.0%), which may reflect the milder preevent visual impairment observed in the Japanese subgroup. Furthermore, 54.5% and 60.0% of cases from North America and Germany, respectively, but none from Japan, experienced a decrease in visual acuity of at least 0.30 logMAR. This is in line with overall findings from a U.S. case series of 26 eyes (included in this review but not in the analysis of individual visual acuity data), which reported that 12 eyes (46%) experienced a more than three-line (0.30 logMAR) decrease in visual acuity at final follow-up.[8] Interestingly, cases in the Japanese and non-Japanese subgroups with no loss of vision showed similar mean changes in visual acuity from preevent levels at the event and at the latest postevent assessment. In addition, higher proportions of male patients and nonocclusive RV events were reported in publications from Japan than in those from North America or Germany.

The use of FA in the diagnosis of RV/RO events was reported for about 70% of the cases included in the review, although the reporting of FA findings and the timing of FA relative to the event and its treatment varied across the cases. Analysis of retinal imaging from a U.S. case series, including color photographs, FA, and optical coherence tomography (OCT), reported that vasculitis affected retinal arteries more widely than retinal veins or choroidal vessels (91%, 79%, and 48% of eyes, respectively).[8] Occlusive vascular disease was observed in 83% of eyes, in line with findings from the current review, and imaging showed evidence of ischemia in 88% of eyes.[8] Multiple imaging measures (slit-lamp examination, dilated fundoscopy, and OCT) are recommended before and after brolucizumab injection to assess for IOI, with further investigation for RV and RO using wide-field FA recommended if IOI is detected.[31] Recent publications have reported the use of OCT angiography to evaluate

Table 4. Patient Characteristics, Event Details, and Treatment, by Subgroup According to Visual Acuity Outcome

	North America		Japan		Non-Japan		All Countries/Regions	
	No VA Loss*	VA Loss†	No VA Loss*	VA Loss†	No VA Loss*	VA Loss†	No VA Loss*	VA Loss†
Number of eyes‡	8 (36.4%)	14 (63.6%)	12 (85.7%)	2 (14.3%)	10 (35.7%)	18 (64.3%)	22 (52.4%)	20 (47.6%)
Age, years								
Mean (SD)**	74.0 (8.9)	82.7 (7.1)	77.7 (11.2)	77.5 (6.4)	73.3 (8.5)	80.1 (8.2)	75.9 (10.2)	79.7 (7.8)
Sex								
Male	0	0	6 (75.0%)	2 (25.0%)	1 (50.0%)	1 (50.0%)	7 (70.0%)	3 (30.0%)
Female	8 (36.4%)	14 (63.6%)	6 (100%)	0	9 (34.6%)	17 (65.4%)	15 (46.9%)	17 (53.1%)
Country/region								
North America	—	—	—	—	8 (36.4%)	14 (63.6%)	8 (36.4%)	14 (63.6%)
Germany	—	—	—	—	2 (40.0%)	3 (60.0%)	2 (40.0%)	3 (60.0%)
Japan	—	—	—	—	—	—	12 (85.7%)	2 (14.3%)
India	—	—	—	—	0	1 (100%)	0	1 (100%)
Event type								
Occlusive RV	6 (30.0%)	14 (70.0%)	5 (71.4%)	2 (28.6%)	7 (29.2%)	17 (70.8%)	12 (38.7%)	19 (61.3%)
Nonocclusive RV	2 (100%)	0	7 (100%)	0	3 (75.0%)	1 (25.0%)	10 (90.9%)	1 (9.1%)
Previous brolucizumab injections								
1 injection	6 (42.9%)	8 (57.1%)	5 (71.4%)	2 (28.6%)	6 (40.0%)	9 (60.0%)	11 (50.0%)	11 (50.0%)
>1 injection	2 (25.0%)	6 (75.0%)	7 (100%)	0	4 (30.8%)	9 (69.2%)	11 (55.0%)	9 (45.0%)
Time from last brolucizumab injection to event, days§								
Mean (SD)	23.1 (9.5)	18.6 (12.9)	23.2 (8.3)	12.5 (0.7)	21.1 (10.8)	15.9 (12.7)	22.2 (9.3)	15.6 (12.1)
Other previous anti-VEGF therapy¶								
Yes	8 (36.4%)	14 (63.6%)	5 (71.4%)	2 (28.6%)	10 (35.7%)	18 (64.3%)	15 (42.9%)	20 (57.1%)
No	0	0	7 (100%)	0	0	0	7 (100%)	0
Preevent VA, logMAR								
Mean (SD)	0.50 (0.58)	0.41 (0.18)	0.27 (0.34)	0.37 (0.21)	0.47 (0.51)	0.47 (0.27)	0.36 (0.43)	0.46 (0.26)
Median (range)	0.33 (0.10–1.90)	0.35 (0.18–0.88)	0.19 (−0.18–1.22)	0.37 (0.22–0.52)	0.33 (0.10–1.90)	0.40 (0.18–1.10)	0.30 (−0.18–1.90)	0.40 (0.18–1.10)
Preevent VA, Snellen equivalents								
Mean	20/63	20/51	20/37	20/47	20/59	20/59	20/46	20/58
Median (range)	20/43 (20/25 to CF)	20/45 (20/30 to 20/150)	20/31 (20/13 to 20/333)	20/47 (20/33 to 20/66)	20/43 (20/25 to CF)	20/50 (20/30 to 20/250)	20/40 (20/13 to CF)	20/50 (20/30 to 20/250)
At event VA, logMAR								
Mean (SD)	0.61 (0.60)	1.32 (0.75)	0.38 (0.42)	0.72 (0.71)	0.62 (0.56)††	1.48 (0.76)	0.48 (0.49)**	1.40 (0.77)
Median (range)	0.40 (0.10–1.90)	1.45 (0.30–2.30)	0.22 (−0.08–1.30)	0.72 (0.22–1.22)	0.40 (0.10–1.90)†††	1.90 (0.30–2.30)	0.30 (−0.08–1.90)***	1.56 (0.22–2.30)
At event VA, Snellen equivalents								
Mean	20/81	20/418	20/48	20/105	20/83	20/604	20/60	20/500
Median (range)	20/50 (20/25 to CF)	20/564 (20/40 to HM)	20/33 (20/17 to 20/400)	20/105 (20/33 to 20/333)	20/50 (20/25 to CF)	CF (20/40 to HM)	20/40 (20/17 to CF)	20/726 (20/33 to HM)
Mean (SD) change in VA from last preevent score, logMAR								
At event	0.11 (0.24)	0.91 (0.73)	0.11 (0.26)	0.35 (0.49)	0.14 (0.25)††	1.01 (0.70)	0.12 (0.25)**	0.94 (0.71)
At latest postevent VA assessment	−0.05 (0.10)	1.09 (0.70)	−0.10 (0.11)	0.18 (0.00)	−0.04 (0.09)	1.05 (0.69)	−0.07 (0.10)	0.96 (0.71)
Mean change in VA from last preevent score, ETDRS letters								
At event	−5.5	−45.5	−5.5	−17.5	−7	−50.5	−6	−47
At latest postevent VA assessment	2.5	−54.5	5	−9	2	−52.5	3.5	−48

(*continued on next page*)

Table 4. (*Continued*)

	North America		Japan		Non-Japan		All Countries/Regions	
	No VA Loss*	VA Loss†	No VA Loss*	VA Loss†	No VA Loss*	VA Loss†	No VA Loss*	VA Loss†
Treatment								
Topical CS	8 (42.1%)	11 (57.9%)	12 (85.7%)	2 (14.3%)	10 (41.7%)	14 (58.3%)	22 (57.9%)	16 (42.1%)
Ocular CS injection	3 (50.0%)	3 (50.0%)	12 (85.7%)	2 (14.3%)	4 (50.0%)	4 (50.0%)	16 (72.7%)	6 (27.3%)
Pars plana vitrectomy	0	3 (100%)	0	0	0	4 (100%)	0	4 (100%)
Systemic CS	6 (42.9%)	8 (57.1%)	3 (100%)	0	8 (42.1%)	11 (57.9%)	11 (50.0%)	11 (50.0%)

Data are shown as number of eyes (%), unless otherwise indicated; percentages show the proportion of eyes in each subgroup for a given variable.

Data are not shown for the Germany no VA loss and VA loss groups because of the small number of eyes in these subgroups.

*No VA loss was defined as an improvement in VA (decrease of ≥0.10 logMAR [increase of ≥5 ETDRS letters] in VA score) or no change in VA (defined as a change of ±0.00–0.08 logMAR [±0–4 ETDRS letters] in VA score) at the latest postevent assessment compared with the last preevent assessment.

†VA loss was defined as an increase of ≥0.10 logMAR (decrease of ≥5 ETDRS letters) in the latest postevent VA score from the last preevent assessment.

‡Eyes with available preevent and postevent VA data.

**Eyes with available data. All countries/regions: no VA loss, n = 20; VA loss, n = 15. North America: no VA loss, n = 6; VA loss, n = 9. Japan: no VA loss, n = 12; VA loss, n = 2. Non-Japan: no VA loss, n = 8; VA loss, n = 13.

§Time to occurrence of symptoms and/or signs of IOI and/or RV on examination.

¶Excluding brolucizumab.

**n = 21.

††n = 9.

CF, count fingers; CS, corticosteroid; ETDRS, Early Treatment Diabetic Retinopathy Study; HM, hand movement; IOI, intraocular inflammation; logMAR, logarithm of the minimal angle of resolution; RV, retinal vasculitis; SD, standard deviation; VA, visual acuity; VEGF, vascular endothelial growth factor.

changes in retinal capillary perfusion after brolucizumab injection.[32,33]

Cases with no vision loss after the event seemed to be younger and more often presented with nonocclusive events than cases with reduced vision, although statistical analyses were not performed. Adverse event management with ocular CS injection seemed to be more common among eyes with no vision loss, although this may reflect the use of ocular CS injection in less severe cases and in all Japanese cases. Cases from Japan accounted for 55% of all eyes with no vision loss, but only 10% of eyes with reduced visual acuity at follow-up, so differences between cases with no loss of vision and those with reduced vision may also have been influenced by the differing characteristics and/or management of Japanese and non-Japanese cases. Japanese physicians may have benefitted from reports of early experience with brolucizumab in the United States after the earlier approval of brolucizumab in the United States (October 2019) than in Japan (March 2020). This could have increased the vigilance for IOI and RV/RO events among Japanese physicians, which may have contributed to the earlier detection of events in Japan and thereby improved outcomes. Moreover, the cut-off date for the inclusion of publications in this review (June 30, 2021) means that the reported events reflect earlier experiences with brolucizumab in clinical practice. After the reporting of the safety signal for brolucizumab in February 2020, it is likely that measures to ensure the early detection and early treatment of RV/RO events may have improved,[34] which could have led to improvements in outcomes for patients. Physicians should monitor patients carefully and patients should be instructed to report any change in vision without delay.[34] Brolucizumab is contraindicated in patients with active IOI, and patients who experience IOI after brolucizumab should be closely monitored, and brolucizumab treatment should be discontinued in patients who develop RV and/or RO events.[5,6] Almost all (97.1%) of the RV and/or RO events reported in the current review had concurrent IOI.

The reason for sex differences in the presentation of RV and/or RO events in the current review is not fully understood, with several complex factors known to affect observed sex differences in the presentation of inflammatory ocular events.[35] However, it is important to note that in the United States and Germany, age-standardized prevalence of AMD is higher among women than among men.[36] By contrast, in Japan, the prevalence of late AMD has been reported to be higher among men than women, more so in old age,[37] and men were found to have a significantly higher incidence of late AMD than women.[38] This may be related to pachychoroid, which is more prevalent in Asians than in Caucasians and may be involved in the development of nAMD, particularly among Asian patients. Pachychoroid is more common in men than in women, which may

contribute to the higher incidence of late AMD in men than in women in Japan.[39] However, the incidence of IOI after brolucizumab injection has been reported to be higher for women than for men in Japan.[40] Furthermore, a higher incidence of brolucizumab-related IOI has been reported in Japanese patients than in patients from other racial groups.[41,42]

Real-world cases of RV and/or RO after brolucizumab treatment for nAMD have been evaluated in a retrospective cohort study using two large U.S. health care databases (the Intelligent Research in Sight [IRIS] Registry and Komodo Healthcare Map [KHM]).[11] For eyes that had an RV and/or RO event, median time to the event was 36 days and 47 days from the last injection, and 42 days and 66 days from the first injection, for the IRIS Registry and KHM, respectively.[11] This is longer than observed for cases reported in the current analysis (median of 17 days and 28 days, respectively), and may reflect the selective reporting of RV and/or RO events that occur earlier. Overall, 50.9% (IRIS Registry) and 55.6% (KHM) of RV and/or RO events occurred after one brolucizumab injection.[11] This compares with 45.7% of events in the current analysis. Multivariate analysis showed that previous IOI and/or RO in the preceding 12 months and female sex were independent risk factors for an increased incidence of an RV and/or RO event in the 6 months after the first brolucizumab injection.[11] Age and previous anti-VEGF treatment were not associated with RV and/or RO occurrence.[11] Findings from the IRIS Registry and KHM analyses and our review are consistent in suggesting an increased risk of RV and/or RO events in women. However, in Japan, more men than women have nAMD, which could account for the more than 20% of men with RV and/or RO events in our review.

RV and/or RO events after brolucizumab treatment have also been evaluated in a *post hoc* analysis of the HAWK and HARRIER studies performed by the SRC. In this analysis, the SRC reported an overall incidence of IOI of 4.6% with brolucizumab, which was similar to the incidence of 4.4% reported by the study investigators.[10,43] Incidences were 3.3% for IOI with RV, 2.1% for IOI with RV and RO, and 0.74% for moderate or severe visual acuity loss associated with IOI.[43] In the original analysis, the study investigators reported an overall incidence of 1.4% for ocular arterial thromboembolic events (ATE) with brolucizumab therapy, with 0.9% of patients experiencing retinal artery occlusion (RAO).[4] Although the numbers of ATE and RAO cases were lower than those of RO events reported by the SRC, the findings are not directly comparable. The Medical Dictionary for Regulatory Activities (MedDRA) terms used to code adverse events in HAWK and HARRIER did not include codes for RO or RV, so investigators could have used a range of MedDRA terms to describe RO and RV events.[43] Furthermore, the increased monitoring and lack of fully flexible injection intervals in the HAWK and HARRIER studies suggested that the findings may not be fully representative of the safety profile in real-world practice. There is the potential for sex and racial differences in the incidence of brolucizumab-related IOI, with some evidence suggesting a higher incidence in women than in men and in Japanese patients than in patients from other racial groups.[5,41,42,44]

Strengths of the current review include the broad, systematic literature searches and the inclusion of non-English language publications. Another strength is the inclusion of additional information about each case supplied by the authors themselves when available; authors from 10 publications (52.6%) responded to our data request, including all of the authors from Japan. This provided valuable data about the events beyond what was reported in the original publications, particularly regarding longer-term patient outcomes, which were typically limited in the original published data. One limitation of this systematic review is that the data are mainly derived from case series and case reports, which were reported spontaneously at the investigator's discretion, so may not be representative of the patient population as a whole. Furthermore, the reporting of events was heterogeneous across the publications. The extent of the information varied widely across the cases, with only limited data available for some measures, such as medical history and medication exposures. In addition, individual patient data were not reported in all publications, reducing the number of eyes available for patient-level analysis; for example, individual visual acuity data were only available for about two-thirds of eyes. The lack of individual data for all cases also raises the possibility that some cases could potentially have appeared in multiple publications. However, analysis of visual acuity data was confined to cases for which individual data were available, and a review of patient and eye details suggested no overlap between the cases included in these analyses. The lack of retinal imaging data is also a limitation. Another potential limitation is the degree of variability used to define no change in vision between preevent and postevent assessments. A loss in visual acuity of as many as four ETDRS letters (0.08 logMAR) could represent a meaningful change in vision for some patients.

In conclusion, this systematic review of RV and/or RO events after brolucizumab treatment for nAMD from real-world clinical practice showed that most evaluated events occurred in women. At the latest follow-up among eyes with recorded visual assessments, approximately half of events were associated with loss of visual acuity, with approximately one-third of all cases

experiencing a reduction in visual acuity of at least 0.30 logMAR (15 ETDRS letters). Of note, there did seem to be regional variations in event characteristics and visual outcomes, with Japanese cases showing milder preevent visual impairment and lower rates of vision loss compared with cases from North America and Germany. Analysis suggests that younger age and nonocclusive events may be associated with an increased likelihood of vision recovery. This information may prove useful in increasing our understanding of these events and their management in routine clinical practice.

Key words: anti-vascular endothelial growth factor therapy, brolucizumab, intraocular inflammation, neovascular age-related macular degeneration, real-world evidence, retinal vascular occlusion, retinal vasculitis.

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