scientific reports

Check for updates

OPEN

Incidence of intraocular inflammation and its risk factors in patients treated with brolucizumab: a nationwide cohort study

Hyo Song Park[1,2,6], Seung Won Lee[3,6], Hyunjin Park[4], Nang Kyeong Lee[5], Yong Joon Kim[4]✉, Christopher Seungkyu Lee[4], Suk Ho Byeon[4] & Sung Soo Kim[4]✉

This study aimed to evaluate the incidence of clinically significant intraocular inflammation (csIOI) after treatment with intravitreal injection (IVI) of brolucizumab and identify csIOI risk factors. We categorized 60,966 South Korean patients from a nationwide population-based cohort into 4 groups: groups 1 (Ranibizumab), 2 (Aflibercept), 3 (Brolucizumab), and 4 (switched to brolucizumab). We used the Kaplan–Meier method to estimate the cumulative incidence of csIOI in each group and calculated the hazard ratios (HRs) and 95% confidence intervals (CIs). We constructed a multivariate model using forward selection methods to identify risk factors for csIOI. The cumulative incidence of csIOI within 180 days of the index date in groups 1, 2, 3, and 4 was 0.36% (67/18,537), 0.49% (186/37,951), 3.47% (38/1,095), and 3.69% (125/3,383), respectively. Multivariate analysis revealed a significant increase in csIOI risk in groups 3 (HR 11.08, 95% CI 7.42–16.53, $P < 0.001$) and 4 (HR 10.40, 95% CI 7.67–14.09, $P < 0.001$). History of retinal vascular occlusion (HR 1.56, 95% CI 1.01–2.40, $P = 0.043$) significantly increased csIOI risk after brolucizumab IVI treatment; female sex (HR 0.78, 95% CI 0.64–0.96, $p = 0.020$) and diabetes (HR 0.72, 95% CI 0.58–0.90, $p = 0.004$) decreased the risk. csIOI incidence was higher after brolucizumab IVI treatment than after ranibizumab and aflibercept IVI treatment. Retinal vein occlusion history, female sex, and diabetes are associated with csIOI after brolucizumab IVI treatment.

Keywords Intraocular inflammation, Brolucizumab, Anti-VEGF

Brolucizumab (Beovu®) is one of the newer anti-VEGF agents introduced for treating neovascular age-related macular degeneration (nAMD). Owing to its small molecular weight and long-lasting effects compared with those of aflibercept, brolucizumab has shown high efficacy in treating subretinal fluid or pigment epithelial detachment, causing vision and macular thickness improvement[1].

However, intraocular inflammation (IOI) incidence of varying severity was reported after treatment with intravitreal injection of brolucizumab (brolucizumab IVI) following the initial pivotal trials[2–5]. Consequently, the initial trial results were revisited. A post hoc review of the HAWK and HARRIER studies revealed that the incidence of definite/probable IOI, IOI with vasculitis, and IOI with vasculitis and occlusion after IVI brolucizumab treatment was 4.6%, 3.3%, and 2.1%, respectively[6]. Several other studies were reported, but most early reports on this topic are post hoc analyses of initial clinical trials or retrospective studies with limited cases.

Therefore, we aimed to conduct a nationwide cohort study to determine the incidence of clinically significant IOI (csIOI) after brolucizumab IVI treatment and identify the associated risk factors using the Korean National

[1]Department of Ophthalmology, College of Medicine, Soonchunhyang University, Cheonan, South Korea. [2]Department of Ophthalmology, Soonchunhyang University Hospital Bucheon, Bucheon, South Korea. [3]Department of Precision Medicine, Sungkyunkwan University School of Medicine, Suwon, South Korea. [4]The Institute of Vision Research, Department of Ophthalmology, Yonsei University College of Medicine, Seoul, South Korea. [5]Department of Computer Science and Engineering, Sungkyunkwan University, Suwon, South Korea. [6]Hyo Song Park and Seung Won Lee contributed equally to this manuscript and are co-first authors ✉email: kyjcolor@yuhs.ac; SEMEKIM@yuhs.ac

Health Insurance claims-based big data. Furthermore, we aimed to compare csIOI incidence after brolucizumab IVI treatment in treatment-naive patients with nAMD and patients who switched from ranibizumab or aflibercept to brolucizumab.

Methods

Ethics statements

This study was conducted with the approval of the Health Insurance Review and Assessment (HIRA) Deliberative Committee (approval number: M20221011001). The use of the national health claims data was approved by the Institutional Review Board (IRB)/Ethics Committee of Severance Hospital, Yonsei University Health System (IRB approval number: 4-2023-1031) and the requirement for obtaining informed consent was waived owing to the retrospective study design and use of de-identified data. This study was conducted following the tenets of the Declaration of Helsinki.

Data source

Data from the Korean National Health Insurance Claims-based database were obtained through the Healthcare Bigdata Hub of the Health Insurance Review & Assessment Service of Korea (https://opendata.hira.or.kr/). The National Health Insurance Claims-based database comprises claims data for > 97% of the Korean population, including demographic information, inpatient and outpatient healthcare visits, prescriptions, diagnoses, and procedures. The data can be used solely for policy and academic research purposes according to the National Health Insurance Act. The data were provided by the Government of Korea upon request; all patient data were anonymized before distribution to ensure patient confidentiality.

Study population

We obtained data on patients diagnosed with nAMD (International Standard Classification of Diseases [ICD]-10 code [H35.31] and registration code [V201]) between January 1, 2008, and August 31, 2022. The "Registration Codes for Special Calculation Rate" is a distinct code system used in South Korea, designated for diseases that may have high treatment costs to alleviate patient financial burdens. The registration code (V201) is typically assigned on the nAMD diagnosis date when anti-VEGF IVI treatment is prescribed. (see Supplementary Table S1)

The initial dataset included 167,752 patients, and patients who did not meet the inclusion criteria were excluded (Fig. 1). We excluded patients diagnosed with nAMD on or before December 31, 2015 ($n = 77{,}183$) and set the period until December 31, 2015, as the washout period. The data used for this study were per-patient based; the possible effect of patients with bilateral disease was minimized by excluding patients administered two or more of ranibizumab, aflibercept or brolucizumab on the same day.

Exposures and outcomes

We divided the eligible patients ($n = 60{,}966$) into four groups based on the anti-VEGF treatment (Fig. 1) type for final analysis. Group 1 ($n = 18{,}537$), group 2 ($n = 37{,}951$), group 3 ($n = 1{,}095$), and group 4 ($n = 3{,}383$) included patients who were treated with ranibizumab initially, aflibercept initially, brolucizumab initially, and ranibizumab or aflibercept initially but received brolucizumab subsequently, respectively. The index date for groups 1–3 was the date of the first anti-VEGF treatment. However, the index date for group 4 was the date of the initial brolucizumab treatment. Bevacizumab was excluded from this study as it is not currently reimbursed by national insurance in South Korea.

We defined csIOI as a systemic steroid or triamcinolone periocular/intraocular injection administered by an ophthalmologist (see Supplementary Table S2). We excluded patients who received topical steroids after IVI as they are often prescribed as a prophylactic for milder IOI immediately after IVI. Cases where csIOI occurred on the day of anti-VEGF injection were excluded as it was considered a preventive treatment.

The primary outcome was the cumulative incidence of csIOI in each group from the index date to day 180 after treatment initiation. The secondary outcome was the risk factors for csIOI incidence after treatment with IVI anti-VEGF.

Covariates

We collected information regarding the age, sex, socioeconomic status (household income: high; highest 30%/middle; 30–70%/low; lowest 30%), and residential area (urban/rural) of the patients from the insurance eligibility data. Additionally, we collected information regarding the presence of comorbid diseases, including rheumatic and non-rheumatic autoimmune diseases, hypertension, DM, dyslipidemia, ischemic stroke, transient ischemic attack, hemorrhagic stroke, myocardial infarction, chronic kidney disease (CKD), malignancy, hyperthyroidism, hypothyroidism, chronic liver disease, and chronic obstructive pulmonary disease (COPD). We evaluated the presence of comorbidities only in cases wherein the ICD-10 codes of ≥ 2 of the same diagnoses were recorded at different visits (see Supplementary Table S2). Regarding ocular comorbidities, the affected eye did not necessarily pertain to the eye being treated with anti-VEGF agent due to limited data available.

Statistics

The baseline demographic characteristics are presented as the mean ± standard deviation for frequency (percentage). We followed up patients from the index date to whichever of the following events occurred first: 180 days after the index date, 60 days after the last anti-VEGF injection, the onset of csIOI or death, or August 31, 2022. Any steroid prescription for these patients provided 60 days after the last anti-VEGF injection was considered uveitis unrelated to anti-VEGF. We used the Kaplan–Meier method to estimate the cumulative incidence of csIOI for each group. We calculated the hazard ratios (HRs) and 95% confidence intervals (CIs)

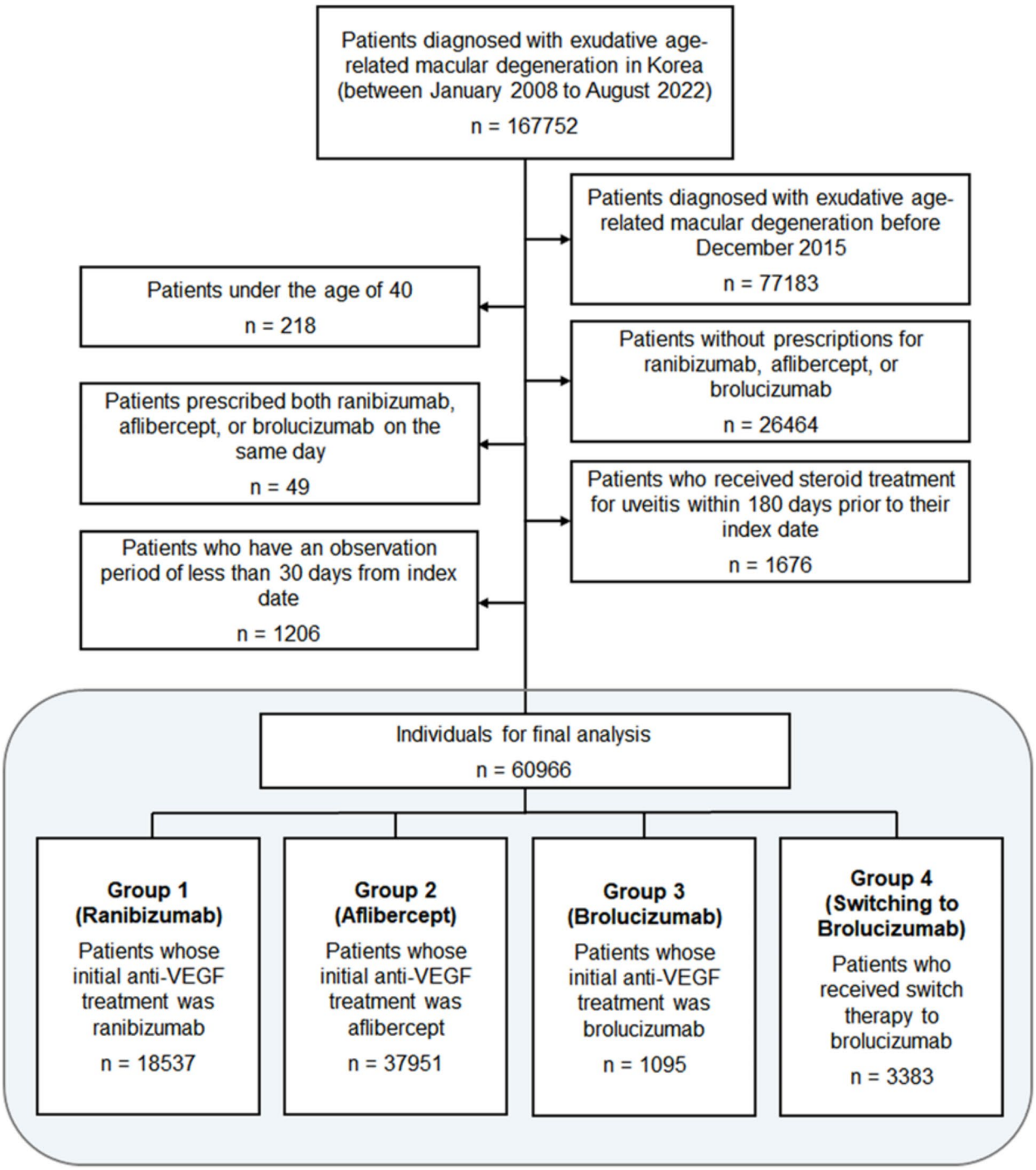


Fig. 1. Flowchart depicting the cohort selection process for this study.

for each group and subgroup based on the Poisson distribution for csIOI using Cox proportional hazards models, with Group 1 (ranibizumab) as the reference. We adjusted the HRs for age; sex; comorbidities, including hypertension, diabetes, dyslipidemia, CKD, chronic liver disease, malignancy, autoimmune disease; and history of noninfectious uveitis and RVO. We confirmed the adequacy of the proportional hazard assumption using log-minus-log survival plots and Schoenfeld residuals.

Finally, we conducted univariate and multivariate analyses to identify the risk factors for csIOI incidence after IVI brolucizumab treatment and constructed a multivariable Cox model using the forward selection method. The criterion for variable selection was based on the residual chi-square. The final model retained the following variables among the 16 variables that were considered initially: age, sex, hypertension, DM, hypothyroidism,

COPD, autoimmune diseases, and history of noninfectious uveitis and RVO. The model achieved a significance level with a P-value of 0.0016.

We performed all statistical analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) and considered a P-value < 0.05 significant.

Results

Baseline demographics

The final analysis comprised 60,966 patients divided into four groups based on the anti-VEGF agent used for initial treatment (Fig. 1). The number of patients aged > 65 years (65.9%) in group 4 was lesser than that in groups 2 (74.1%), 3 (75.2%), and 1 (80.0%) (Table 1). The number of males was higher than the number of females in groups 2 (62.8%), 3 (68.1%), and 4 (69.5%); the number of male and female patients was comparable in group 1 (53.6%). Significant differences were observed among the groups in terms of the number of patients with comorbidities (including autoimmune diseases). The number of patients with a history of non-infectious uveitis in group 4 (0.6%) was lesser than that in groups 1, 2, and 3; however, the number of patients with a history of RVO (5.8%), recent cataract surgery (26.5%), and trans pars plana vitrectomy (5.3%) was higher than that in groups 1, 2, and 3.

The median number of injections over 180 days after the first IVI in groups 1, 2, 3, and 4 was three (interquartile range [IQR], 3–4), three (IQR, 3–4), three (IQR, 2–3), and two (IQR, 2–3), respectively (see Supplementary Table S3). Thus, group 4 had the lowest median number of injections. The number of patients who received ≥ 3 injections was the highest in group 2 (82.1%), followed by group 1 (79.6%) and group 3 (65.3%); the number was the lowest in group 4 (40.4%). Compared with the other agents, brolucizumab was used more frequently in primary care centers (group 3, 37.7%) than in secondary or tertiary centers (group 1; 26.2%, group 2; 25.0%, group 4; 26.7%). The median number of injections administered before initiating brolucizumab treatment was nine (IQR, 5–16) in group 4. The mean interval between the first IVI anti-VEGF to the first IVI brolucizumab was 899 ± 589 days in group 4, whereas the mean interval between the last IVI anti-VEGF other than brolucizumab to the first IVI brolucizumab was 136 ± 243 days.

	Group 1 (ranibizumab)	Group 2 (aflibercept)	Group 3 (brolucizumab)	Group 4 (Switched to brolucizumab)
Total N	18,537	37,951	1095	3383
Demographic age (years)				
40–49	160 (0.9)	340 (0.9)	11 (1)	38 (1.1)
50–64	3544 (19.1)	9471 (25)	261 (23.8)	1116 (33)
≥ 65	14,833 (80)	28,140 (74.1)	823 (75.2)	2229 (65.9)
Sex				
Male	9930 (53.6)	23,817 (62.8)	746 (68.1)	2351 (69.5)
Female	8607 (46.4)	14,134 (37.2)	349 (31.9)	1032 (30.5)
Comorbidities				
Hypertension	12,168 (65.6)	23,541 (62)	688 (62.8)	2084 (61.6)
Diabetes	7260 (39.2)	14,015 (36.9)	389 (35.5)	1325 (39.2)
Dyslipidemia	11,944 (64.4)	23,571 (62.1)	738 (67.4)	2314 (68.4)
Ischemic stroke	1681 (9.1)	2970 (7.8)	77 (7)	230 (6.8)
Transient ischemic attack	522 (2.8)	1031 (2.7)	32 (2.9)	99 (2.9)
Hemorrhagic stroke	129 (0.7)	260 (0.7)	8 (0.7)	27 (0.8)
Myocardial infarction	428 (2.3)	807 (2.1)	23 (2.1)	83 (2.6)
Chronic kidney disease	803 (4.3)	1610 (4.2)	44 (4)	173 (5.1)
Malignancy	2069 (11.2)	4324 (11.4)	141 (12.9)	453 (13.4)
Hyperthyroidism	304 (1.6)	658 (1.7)	17 (1.6)	64 (1.9)
Hypothyroidism	1320 (7.1)	2414 (6.4)	64 (5.8)	230 (6.8)
Chronic liver disease	2038 (11)	4127 (10.9)	140 (12.8)	383 (11.3)
COPD	1354 (7.3)	2634 (6.9)	79 (7.2)	248 (7.3)
Autoimmune disease				
None	16,654 (89.8)	34,471 (90.8)	992 (90.6)	3061 (90.5)
Rheumatic autoimmune	1744 (9.4)	3200 (8.4)	98 (8.9)	291 (8.6)
Non-rheumatic autoimmune	139 (0.7)	280 (0.7)	5 (0.5)	31 (0.9)
Previous ocular history				
Non-infectious uveitis history	215 (1.2)	490 (1.3)	14 (1.3)	20 (0.6)
Retinal vein occlusion	654 (3.5)	1311 (3.5)	53 (4.8)	195 (5.8)

Table 1. Baseline demographic characteristics of each population group. COPD, chronic obstructive pulmonary disease.

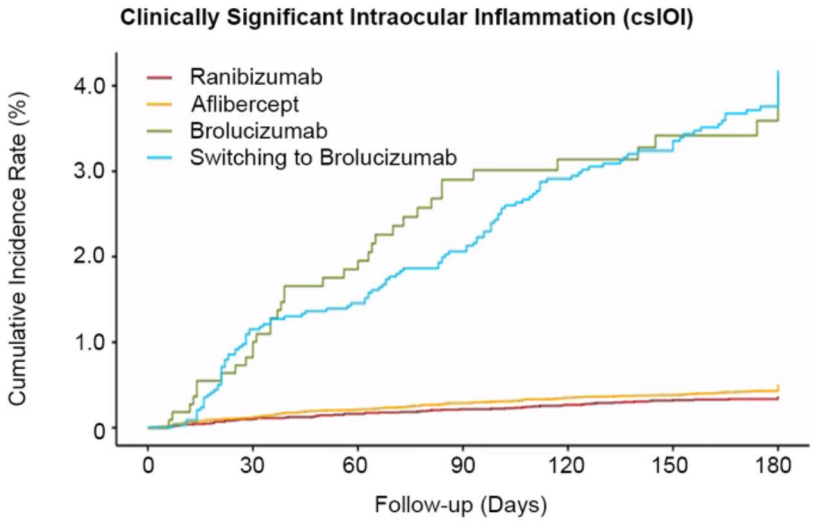
Incidence of csIOI after treatment with IVI anti-VEGF agents

The cumulative incidence of csIOI within 180 days of the index date in groups 1, 2, 3, and 4 was 0.36% (67/18,537), 0.49% (186/37,951), 3.47% (38/1,095), and 3.69% (125/3,383), respectively (Fig. 2). CsIOI incidence in group 3 was significantly higher than that in groups 1 and 2 ($P<0.001$ [groups 1 and 3], $P<0.001$ [groups 2 and 3]; see Supplementary Table S4). The median interval between the index date and the date of csIOI incidence in groups 1, 2, 3, and 4 was 72 days (IQR, 25–125 days), 74 days (IQR, 30–139), 53 days (IQR, 30–84), and 83 days (IQR, 26–121), respectively. The median interval between the index date and the date of csIOI incidence in group 3 was significantly shorter than that in groups 1, 2, and 4 ($P<0.001$ [groups 1 and 3], $P<0.001$ [groups 2 and 3], and $P<0.001$ [groups 3 and 4]). The number of injections administered before csIOI incidence differed among the groups. Groups 3 and 4 included a higher number of patients who developed csIOI immediately after the first IVI brolucizumab (group 3, 44.7%; group 4, 47.2%). Contrarily, most patients in groups 1 and 2 developed csIOI after the third or subsequent injections (group 1, 40.3%; Group 2, 44.6%).

HRs for csIOI incidence using the incidence rate of group 1 as the reference were 1.33 (95% CI 1.01–1.76), 11.08 (95% CI 7.42–16.53), and 10.40 (95% CI 7.67–14.09) in groups 2, 3, and 4, respectively (Fig. 3). HR for csIOI incidence in group 1 was significantly lower than those in groups 2, 3, and 4 ($P=0.045$ [group 2], $P<0.0001$ [group 3] and $P<0.0001$ [group 4]). HRs for csIOI incidence in each sex using the incidence rate of Group 1 as the reference were significantly higher in groups 2, 3, and 4 than that in group 1 (see Supplementary Figure S1). The monthly incidence rate of csIOI events was higher following brolucizumab treatment (group 3 + group 4), with approximately 1–2% of cases per injection, compared with < 0.5% of cases per injection following treatment with ranibizumab or aflibercept (see Supplementary Figure S2). The monthly incidence rate of csIOI events in groups 3 and 4 is presented in Supplementary Figure S3. The monthly incidence rate of csIOI events per injection ratio varied between April 2021 and July 2022; however, we observed no trend of increase or decrease over time.

Risk factors for csIOI after IVI brolucizumab

We assessed the risk factors for csIOI incidence after IVI brolucizumab treatment using univariate and multivariate analysis and analyzed the patients in groups 3 and 4 together (1,095 [Group 3] + 3,424 [Group 4] = 4,478). Univariate analysis revealed that a history of malignancy (HR = 1.33 [95% CI 1.02–1.75], $P=0.038$) and RVO (HR = 1.49 [0.97–2.29], $P=0.070$) had significantly higher HRs for csIOI incidence (Table 2). Conversely, female sex (HR = 0.77 [0.63–0.95], $P=0.013$), history of hypertension (HR = 0.77 [0.64–0.94], $P=0.010$), and DM (HR = 0.69 [0.56–0.85], $P=0.001$) had lower HRs for csIOI incidence. Multivariate analysis



Number at risk

Ranibizumab	18537	18519	18324	18131	17922	17650	17463
Aflibercept	37951	37907	37257	36496	35770	35030	34362
Brolucizumab	1095	1086	978	869	765	653	549
Switching to Brolucizumab	3383	3344	3155	2957	2728	2495	2268

Cumulative number of events

Ranibizumab	0	19	30	40	49	59	67
Aflibercept	0	47	81	108	131	142	186
Brolucizumab	0	11	21	30	32	34	38
Switching to Brolucizumab	0	39	49	68	93	105	125

Fig. 2. Cumulative incidence rates, number of patients at risk, and cumulative number of events of clinically significant IOI (csIOI) within 60 days after the index date.

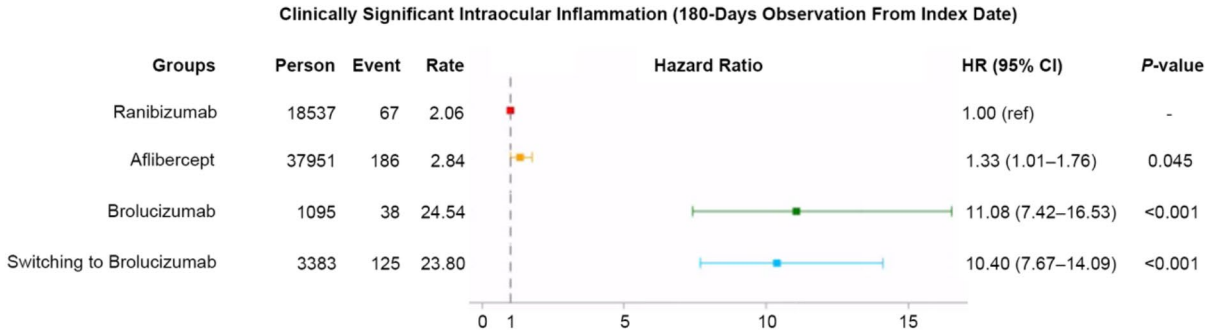


Fig. 3. Hazard ratios for clinically significant IOI (csIOI) within 60 days after the index date in each sex using the incidence rates of Group 1 as a reference. The rate is demonstrated in 100,000 person-year. (CI, confidence interval; HR, hazard ratio, N/A, not available; Ref; reference)

	Univariable			Multivariable		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (years)						
< 65	1.00 (ref)			1.00 (ref)		
≥ 65	0.83	0.67–1.03	0.084	0.92	0.73–1.15	0.445
Sex						
Male	1.00 (ref)			1.00 (ref)		
Female	0.77	0.63–0.95	0.013	0.78	0.64–0.96	0.020
Systemic diseases						
Hypertension	0.77	0.64–0.94	0.010	0.86	0.70–1.06	0.148
Diabetes	0.69	0.56–0.85	0.001	0.72	0.58–0.90	0.004
Dyslipidemia	0.97	0.79–1.18	0.743			
Ischemic stroke	0.85	0.58–1.23	0.382			
Transient ischemic attack	1.04	0.59–1.85	0.885			
Hemorrhagic stroke	0.69	0.17–2.76	0.599			
Myocardial infarction	0.76	0.36–1.61	0.477			
Chronic kidney disease	1.07	0.68–1.70	0.772			
Malignancy	1.33	1.02–1.75	0.038			
Hyperthyroidism	1.27	0.66–2.46	0.475			
Hypothyroidism	0.79	0.52–1.22	0.289	0.91	0.59–1.41	0.678
Chronic liver disease	0.82	0.59–1.14	0.238			
COPD	1.06	0.73–1.52	0.768	1.07	0.74–1.55	0.719
Autoimmune diseases	0.93	0.66–1.30	0.675	1.02	0.73–1.44	0.898
Previous ocular history						
Noninfectious uveitis history	0.73	0.27–1.95	0.530	0.69	0.26–1.86	0.467
Retinal vein occlusion	1.49	0.97–2.29	0.070	1.56	1.01–2.40	0.043

Table 2. Possible risk factors for csIOI after treatment with IVI brolucizumab identified using univariate and multivariate analysis. CI, confidence interval; HR, hazard ratio; COPD, chronic obstructive pulmonary disease; IVI, intravitreal injection.

including variables that were significant ($P < 0.10$) in univariable analysis revealed that RVO history (HR = 1.56 [1.01–2.40], $P = 0.043$) had significantly higher HRs for csIOI incidence. Contrarily, female sex (HR = 0.78 [0.64–0.96], $P = 0.020$) and DM history (HR = 0.72 [0.58–0.90], $P = 0.004$) had lower HRs for csIOI incidence. The result of multivariate analysis including all variables is presented in Supplementary Table S5.

Recurrence of csIOI following re-treatment with brolucizumab

csIOI events occurred in 163 patients (3.6%) among all patients who received brolucizumab IVI (Group 3 + Group 4, $n = 4,478$). Among the 163 patients, 46 patients received brolucizumab IVI again after the csIOI event (46/163 = 28.2%); 28 patients among the 46 patients who received brolucizumab IVI again developed csIOI again (28/46 = 60.9%).

Discussion

This study shows that csIOI incidence rate among patients who were brolucizumab-naive and those switched-to-brolucizumab (groups 3 and 4) was > 3%, whereas the incidence rate was < 0.5% among patients who received IVI ranibizumab and IVI aflibercept (groups 1 and 2). The incidence rates of csIOI after IVI brolucizumab treatment were consistent with the 3% incidence rate reported in studies that evaluated IOI incidence with retinal involvement (retinal vasculitis and/or retinal occlusion)[7,8].

We found that the time interval between the last IVI and csIOI incidence was significantly shorter in the brolucizumab-naive group (group 3) than that in the switched-to-brolucizumab group (group 4). This indicates the possibility of earlier presentation of csIOI in patients receiving IVI more frequently, as treatment-naive patients usually receive three loading schedules of IVI. However, we observed no difference in the final cumulative incidence of csIOI 180 days after treatment with IVI between the two groups, indicating that prolonging the duration until brolucizumab IVI only may not be sufficient to prevent csIOI incidence. Consequently, it is plausible that at-risk patients with potential risk factors developed severe IOI earlier during the study period.

We observed some discrepancies between our results and those of previous studies in terms of the risk factors for csIOI after IVI brolucizumab treatment. Previous reports identified a history of IOI and/or RVO, female sex, old age, DM, SHRM, and macular atrophy as risk factors for IOI after IVI brolucizumab treatment[9–13]. Khanani et al. reviewed > 20,000 eyes from two large healthcare databases (IRIS and Komodo) and concluded that a history of IOI or RVO within 12 months of initiating brolucizumab treatment caused an increased risk of developing IOI and/or retinal occlusion[12]. However, the extent of the potential overlap between these two registries could not be determined[12]. Consistent with Khanani et al., our study showed that RVO history was the only factor that caused a higher risk of developing csIOI after brolucizumab IVI treatment. Studies have identified female sex as a potential risk factor for IOI after brolucizumab treatment. The higher preponderance of noninfectious uveitis and autoimmune disorders in women has been hypothesized to play a role[11,12]. However, female sex was associated with a lower risk of retinal vasculitis and/or RVO in the study by Khanani et al., which is consistent with the findings of our study wherein female sex was associated with a lower risk of developing csIOI.

A Japanese study identified DM as a risk factor for IOI; however, DM was associated with a lower risk of developing csIOI in our study[13]. This difference may be attributed to some of the early studies on the risk factors of IOI having a small sample size of 80–150 patients[9,11,13]. Additionally, phase 3 trials for brolucizumab in patients with diabetic macular edema (KESTREL and KITE) reported a lower incidence of retinal vasculitis and RVO than the trials for nAMD (HAWK and HARRIER). However, the findings are not directly comparable owing to the differences in injection schedule and population (retinal vasculitis and/or RVO; 2.1% (KESTREL 6 mg arm), 0.6% (KITE 6 mg arm) vs. 3.3% (HAWK and HARRIER)[6,14]. Consequently, further studies with larger population data must be conducted to identify the potential risk factors for IOI after brolucizumab IVI.

Our study showed that 28% of patients who developed csIOI after brolucizumab IVI treatment were re-treated with brolucizumab, and 61% of these patients experienced csIOI recurrence. This indicates that patients at risk of developing csIOI after brolucizumab IVI treatment have a high risk of csIOI recurrence when re-treated with brolucizumab. However, we were unable to completely evaluate the clinical characteristics of recurrence after re-treatment with brolucizumab in such patients, as we excluded patients with milder IOIs and anterior inflammation that could be treated with topical steroids. Therefore, brolucizumab use should be suspended in patients who develop csIOI even after the symptoms have subsided to prevent recurrence.

Nonetheless, this study has some limitations. First, as the data were provided from a national database by request, patients with bilateral disease might have influenced the results as this was per-patient data, not per-eye data. However, this influence was minimized by excluding possible patients with bilateral disease while constructing the cohort. Second, some of the demographic characteristics were heterogeneous owing to the retrospective nature of this study. Although these factors were adjusted for analyses, these may have limited the interpretation of the results of the analyses. Third, we defined csIOI based on the prescription of steroids and not by the medical records or diagnostic codes. The definition of csIOI hindered us from evaluating milder cases of IOI with only anterior inflammation, which accounts for most IOI cases after IVI brolucizumab treatment. Therefore, we were unable to assess the characteristics, severity, and treatment course of csIOI in relation to IVI patterns other than the incidence. Lastly, some of the neuroinflammatory diseases including multiple sclerosis which could have been associated with csIOI were not included and assessed in this study. Although the incidence of such diseases in uveitis seems to be low according to a previous study, including them might have provided the broader picture of the association of csIOI with other diseases.

In conclusion, the findings of this large cohort study suggest that csIOI incidence after IVI brolucizumab treatment was significantly higher than that after treatment with ranibizumab or aflibercept. We found that RVO history was associated with a higher risk of developing csIOI after IVI brolucizumab treatment. Understanding such possibilities plays a critical role in formulating appropriate treatment plans for patients with nAMD using brolucizumab who have risk factors for csIOI. Further prospective studies with larger and demographically homogeneous population groups must be conducted in the future to validate the findings of this study.

Data availability

The data that support the findings of this study are available from Healthcare Bigdata Hub of the Health Insurance Review & Assessment Service of Korea (https://opendata.hira.or.kr/) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Healthcare Bigdata Hub of the Health Insurance Review & Assessment Service of Korea (https://opendata.hira.or.kr/). Please contact Yong Joon Kim (kyjcolor@yuhs.ac) if there is any further question or request regarding the data.

Received: 19 July 2024; Accepted: 20 September 2024
Published online: 02 October 2024

References

1. Dugel, P. U. et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. **127**, 72–84. https://doi.org/10.1016/j.ophtha.2019.04.017 (2020).
2. Baumal, C. R. et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of Brolucizumab. *Ophthalmology*. **127**, 1345–1359. https://doi.org/10.1016/j.ophtha.2020.04.017 (2020).
3. Haug, S. J. et al. Retinal arterial occlusive vasculitis following intravitreal brolucizumab administration. *Am. J. Ophthalmol. Case Rep.* **18**, 100680. https://doi.org/10.1016/j.ajoc.2020.100680 (2020).
4. Iyer, P. G. et al. Brolucizumab-related retinal vasculitis with exacerbation following ranibizumab retreatment: a clinicopathologic case study. *Am. J. Ophthalmol. Case Rep.* **20**, 100989. https://doi.org/10.1016/j.ajoc.2020.100989 (2020).
5. Jain, A. et al. Severe vision loss secondary to retinal arteriolar occlusions after multiple intravitreal brolucizumab administrations. *Am. J. Ophthalmol. Case Rep.* **18**, 100687. https://doi.org/10.1016/j.ajoc.2020.100687 (2020).
6. Monés, J. et al. Risk of inflammation, retinal vasculitis, and retinal occlusion-related events with Brolucizumab: Post Hoc review of HAWK and HARRIER. *Ophthalmology*. **128**, 1050–1059. https://doi.org/10.1016/j.ophtha.2020.11.011 (2021).
7. Kim, D. J. et al. Short-term safety and efficacy of intravitreal brolucizumab injections for neovascular age-related macular degeneration: a multicenter retrospective real-world study. *Ophthalmologica*. https://doi.org/10.1159/000529410 (2023).
8. Bodaghi, B. et al. Detection and management of intraocular inflammation after brolucizumab treatment for neovascular age-related macular degeneration. *Ophthalmol. Retina*. https://doi.org/10.1016/j.oret.2023.06.009 (2023).
9. Sotani, R. et al. Clinical features and associated factors of intraocular inflammation following intravitreal brolucizumab as switching therapy for neovascular age-related macular degeneration. *Graefes Arch. Clin. Exp. Ophthalmol.* https://doi.org/10.1007/s00417-023-06036-x (2023).
10. Baumal, C. R. Risk factors for intraocular inflammation after brolucizumab treatment. *JAMA Ophthalmol.* **140**, 28–29. https://doi.org/10.1001/jamaophthalmol.2021.4586 (2022).
11. Enríquez, A. B. et al. Early experience with brolucizumab treatment of neovascular age-related macular degeneration. *JAMA Ophthalmol.* **139**, 441–448. https://doi.org/10.1001/jamaophthalmol.2020.7085 (2021).
12. Khanani, A. M. et al. Safety outcomes of Brolucizumab in neovascular age-related macular degeneration: Results from the IRIS registry and komodo healthcare map. *JAMA Ophthalmol.* **140**, 20–28. https://doi.org/10.1001/jamaophthalmol.2021.4585 (2022).
13. Mukai, R., Matsumoto, H. & Akiyama, H. Risk factors for emerging intraocular inflammation after intravitreal brolucizumab injection for age-related macular degeneration. *PLoS One*. **16**, e0259879. https://doi.org/10.1371/journal.pone.0259879 (2021).
14. Wykoff, C. C. et al. KESTREL and KITE Phase 3 studies: 100-week results with brolucizumab in patients with diabetic macular edema. *Am. J. Ophthalmol.* https://doi.org/10.1016/j.ajo.2023.07.012 (2023).

Acknowledgements

None.

Author contributions

Research design, Y.J.K, S.S.K.; Data acquisition and/or research execution, H.S.P., S.W.L., H.J.P., N.K.L., Y.J.K., S.S.K.; Data analysis and/or interpretation, H.S.P., S.W.L., H.J.P., N.K.L., Y.J.K., C.S.L., S.H.B., S.S.K.; Manuscript preparation, H.S.P., S.W.L., N.K.L., Y.J.K., S.S.K. All authors have read and agreed to the published version of the manuscript.

Funding

This research was supported by Basic Science Research Program through the National Research Foundation (NRF) of Korea funded by the Ministry of Education (RS-2023-00238454). This research was also supported a new faculty research seed money grant of Yonsei University College of Medicine for 2024 (2024-32-0061). This work was supported by the Soonchunhyang University Research Fund. The funding organization had no role in the design or conduct of this research.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-73782-1.

Correspondence and requests for materials should be addressed to Y.J.K. or S.S.K.