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ORIGINAL RESEARCH

Systemic Outcomes of Intravitreal Injections of Dexamethasone and Anti-Vascular Endothelial Growth Factor

Tzu-Yi Lin · Yi-Ting Hsieh · Sunir J. Garg · Lee-Jen Chen · Kuan-Jen Chen · Wei-Chi Wu · Chi-Chun Lai · Yih-Shiou Hwang · Eugene Yu-Chuan Kang

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ABSTRACT

Introduction: Intravitreal dexamethasone and anti-vascular endothelial growth factor (anti-VEGF) medications have revolutionized ocular disease management and favorable ocular safety profiles, but few studies have compared their systemic adverse events (SAEs). This study investigated the SAEs of intravitreal dexamethasone and anti-VEGFs by using real-world data.

Methods: This retrospective cohort study sourced medical records from the largest multi-institutional database in Taiwan. Patients who received intravitreal dexamethasone (n = 137) or anti-VEGFs (n = 10,345) between 2014 and 2019 were enrolled. Propensity score matching was performed to achieve homogeneity between the two groups. Subdistribution hazard ratios (SHRs) and 95% confidence intervals (CIs) were calculated using the Fine–Gray model.

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T.-Y. Lin
Department of Education, Linkou Medical Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan

T.-Y. Lin · K.-J. Chen · W.-C. Wu · C.-C. Lai · Y.-S. Hwang (✉) · E. Y.-C. Kang (✉)
College of Medicine, Chang Gung University, Taoyuan, Taiwan
e-mail: yihshiou.hwang@gmail.com

E. Y.-C. Kang
e-mail: yckang0321@gmail.com

Y.-T. Hsieh
Department of Ophthalmology, National Taiwan University Hospital, Taipei, Taiwan

S. J. Garg
MidAtlantic Retina, The Retina Service of Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA, USA

L.-J. Chen
Department of Ophthalmology, Mackay Memorial Hospital, Taipei, Taiwan

K.-J. Chen · W.-C. Wu · Y.-S. Hwang · E. Y.-C. Kang
Department of Ophthalmology, Linkou Medical Center, Chang Gung Memorial Hospital, No. 5, Fu Shin St., Kuei-Shan, Taoyuan 333, Taiwan

C.-C. Lai
Department of Ophthalmology, Chang Gung Memorial Hospital, Keelung, Taiwan

Y.-S. Hwang
Department of Ophthalmology, Jen-Ai Hospital Dali Branch, Taichung, Taiwan

E. Y.-C. Kang
Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan

Y.-S. Hwang
Department of Ophthalmology, Xiamen Chang Gung Memorial Hospital, Xiamen, China

Systemic as well as ocular clinical events and systemic biomarkers after 1-year follow-up were compared.

Results: Both groups demonstrated comparable risks of major cardiac adverse events (SHR 1.57, 95% CI 0.29–8.55), heart failure (SHR 0.62, 95% CI 0.07–5.33), major bleeding (SHR 0.23, 95% CI 0.03–1.77), all-cause admission (SHR 0.73, 95% CI 0.41–1.30), and all-cause death (SHR 2.11, 95% CI 0.35–12.71). There were no significant differences in longitudinal changes in systolic and diastolic blood pressure, glycated hemoglobin, low-density lipoprotein, estimated glomerular filtration rate, or alanine aminotransferase between the groups. Both groups had a similar incidence of cataract surgery. Although the dexamethasone group exhibited a relatively high prevalence of antiglaucomatous medication use, there was not a significantly higher incidence of glaucoma surgery.

Conclusion: Intravitreal dexamethasone and anti-VEGF medications had comparable systemic safety profiles in our study. Both drugs represent efficacious and safe therapies for ocular diseases.

Keywords: Anti-vascular endothelial growth factor; Dexamethasone; Intravitreal injection; Systemic adverse event; Systemic safety

Key Summary Points

Intravitreal dexamethasone and anti-vascular endothelial growth factors (anti-VEGFs) medications have well-established ocular efficacy and safety.

However, less is known about their systemic safety profiles in clinical practice.

The patients receiving intravitreal dexamethasone and anti-VEGF medications showed comparable incidence of systemic adverse events and no significant difference in systemic biomarkers during the 1-year follow-up.

Intravitreal dexamethasone and anti-VEGFs may have comparable profiles of systemic safety in routine care. Both classes of medications could be safely prescribed to patients with ocular diseases.

INTRODUCTION

Intravitreal injections (IVIs) are commonly used for the management of retinal diseases [1–3]. Two major classes of medications administered as IVIs included anti-vascular endothelial growth factor (anti-VEGF) medications and corticosteroids. Intravitreal anti-VEGF medications, including bevacizumab, ranibizumab, and aflibercept, inhibit pathological neovascularization and diminish vascular permeability [4]. These agents serve as effective therapeutics for age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO) [5]. In addition, intravitreal corticosteroids such as intravitreal dexamethasone implants block cytokine production to ameliorate inflammation [6]. The intravitreal dexamethasone implant represents a long-acting treatment of DME, RVO, and posterior noninfectious uveitis [7]. Despite the benefits of intravitreal anti-VEGFs and dexamethasone for treating ocular diseases, their systemic safety profiles have been less well studied.

The issue of systemic adverse events (SAEs) in patients receiving IVIs has been raised in the past decade [8, 9]. Because of the blood–retinal barrier, intravitreal agents can achieve and maintain sufficient intraocular concentrations for therapy [2, 8]. However, systemic diffusion of agents may still occur even if they are administered at relatively low concentrations [8]. In addition, multiple IVIs are often required from chronic diseases such as neovascular AMD (nAMD), DME, RVO, and noninfectious uveitis [9, 10]. Accumulated doses of these agents could alter metabolism and induce SAEs [11, 12]. Studies have revealed that patients receiving anti-VEGF medications through intravenous

chemotherapy occasionally reported proteinuria, hypertension, and arterial thromboembolism [13–15]. A previous study has demonstrated a potential risk of cerebrovascular events in patients receiving intravitreal anti-VEGF injection [16]. However, most studies of intravitreal anti-VEGF medications found favorable systemic safety profiles [5, 17, 18]. Systemic administration of dexamethasone can induce complications such as hyperglycemia [19]. Although most randomized controlled trials (RCTs) have reported rare SAEs in patients who received intravitreal dexamethasone, few studies have compared the safety outcomes of intravitreal dexamethasone and anti-VEGFs [20, 21].

Intravitreal dexamethasone and anti-VEGFs involve distinct molecules and mechanisms; therefore, their effects may differ in terms of the risk of SAEs. Some meta-analyses of RCTs have reported that intravitreal dexamethasone and anti-VEGFs exhibited comparable systemic safety outcomes compared with placebo therapy [22–25]. Moreover, comparative RCTs have demonstrated similar systemic safety profiles for both dexamethasone and anti-VEGFs [20, 26]. Nevertheless, the selected populations and therapeutic protocols used in these studies are different, limiting the generalizability of these outcomes. RCTs are underpowered for identifying meaningful differences in rare SAEs between patients receiving different agents. Moreover, treatment patterns in real-world practice and in RCTs are substantially different in terms of population characteristics. As there have been limited studies on the differences in safety profiles between intravitreal anti-VEGFs and corticosteroids, we used a real-world database to compare the risks of SAEs in patients receiving intravitreal dexamethasone and anti-VEGF medications.

METHODS

Data Source

This was a retrospective cohort study utilizing the Chang Gung Research Database (CGRD). This database contains the electronic medical records from seven medical facilities of the Chang Gung Memorial Hospital (CGMH) system in Taiwan [27]. Demographic data, medication usage, intervention history, laboratory data, imaging reports, and nursing records could be retrieved from the CGRD, which has been established from as early as 2001. Diseases recorded prior to 2016 were diagnosed using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes, whereas those recorded in 2016 or later were diagnosed using both ICD-9-CM and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnostic codes. Published studies have provided the details and validity of the CGRD [27, 28]. Notably, the CGRD includes the information for self-paid procedures, which are not recorded in the National Health Insurance Research Database. This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. This study was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB no. 202200606B1). Written informed consent was waived due to the de-identification and encryption of patient data.

Patient Inclusion

CGMH payment codes were used to identify patients who received either intravitreal dexamethasone (0.7 mg implants; Ozurdex, Allergan, Irvine, CA, USA) (dexamethasone group) or intravitreal anti-VEGF medications (anti-VEGF group) between January 1 2014 and December 31 2019. Anti-VEGFs including bevacizumab (1.25 mg/0.05 mL; Avastin, Genentech, San Francisco, CA, USA), ranibizumab (0.5 mg/0.05 mL; Lucentis, Norvartis, Basel, Switzerland), and aflibercept (2.0 mg/0.05 mL; Eylea, Bayer, Leverkusen, Germany) were used as the active comparators. The new-user design was adopted to minimize selection bias [29]. The study index date was defined as the date of first prescription of the indicated drug. Patients aged younger than 20 years, with prior administration of intravitreal dexamethasone or anti-VEGFs medications at any time point, or with a

history of ocular use of triamcinolone acetonide at any time point were excluded from this study. Additionally, because the treatment of malignancies, such as colorectal and ovarian cancer, may involve anti-VEGFs through intravenous chemotherapy, patients with a history of such malignancies were excluded from enrollment.

Covariate Assessment

The covariates considered in this study were demographics, systemic and ocular comorbidities, and medications at baseline. Demographic data consisted of age, gender, and body mass index. Comorbidities comprised metabolic syndrome (hypertension, diabetes mellitus, and dyslipidemia), cardiovascular disorders (heart failure, ischemic heart disease, and ischemic stroke), and other diseases (chronic kidney disease, chronic obstructive pulmonary disease, and obstructive sleep apnea). The patients were identified as having one of these diseases as comorbidities if they had at least one inpatient department diagnosis or two outpatient department diagnoses with relevant diagnostic codes. Charlson Comorbidity Index scores were calculated to evaluate disease burden [30]. Medications retrieved on the study index date were classified into three categories: antihypertensive, antihyperglycemic, and other medications. Ocular history comprised cataracts, use of antiglaucomatous medication, AMD, diabetic retinopathy, DME, vitreous hemorrhage, uveitis, retinal vessel occlusion, retinal laser, and vitrectomy. The number of ophthalmology outpatient department (OPD) visits during the past 1 year and the number of IVIs during the 1-year follow-up were also collected.

Outcome Definition

The outcomes considered in this study were categorized as clinical events and systemic biomarkers. Clinical events of primary interest included major adverse cardiac events (MACEs), heart failure, thromboembolic events, bleeding events, all-cause hospital admission, and all-cause death. MACEs comprised myocardial infarction, ischemic stroke, and cardiovascular death. Thromboembolic events involved transient ischemic attacks, extremity thromboembolism, and systemic thromboembolism. Bleeding events comprised major bleeding, gastrointestinal bleeding, and intracranial hemorrhage. We also considered the overall complication rate, comprising any one of MACEs, heart failure, thromboembolism events, bleeding events, all-cause admission, and all-cause death. The occurrence of myocardial infarction, ischemic stroke, heart failure, thromboembolic events, and bleeding events was detected in inpatient department records only. The date, place, and cause of death were identified using the Taiwan Death Registry, released by the Taiwan Ministry of Health and Welfare. Systemic biomarkers were systolic blood pressure (SBP), diastolic blood pressure (DBP), glycated hemoglobin (HbA1c), low-density lipoprotein (LDL), estimated glomerular filtration rate (eGFR), and alanine aminotransferase (ALT). Clinical events of secondary interest were ocular outcomes, including glaucoma medication, glaucoma surgery, cataract surgery, and vitrectomy.

The patients were followed until the occurrence of a clinical event, a switch between intravitreal dexamethasone and anti-VEGFs medications, death, last visit recorded in the CGRD, 1 year after the study index date, or December 31 2019. Data on the systemic biomarkers (SBP, DBP, HbA1c, LDL, eGFR, and ALT) were collected every 6 months.

Statistical Analysis

To minimize possible confounders, propensity score matching (PSM) was performed to achieve homogeneity between the dexamethasone and anti-VEGF groups. The propensity score was calculated using a multivariable logistic regression model and represented the predicted probability of certain covariates. The covariates used in the calculation are listed in Table 1. They included possible IVI indications [age-related macular degeneration, diabetic retinopathy, diabetic macular edema (DME), and retinal vessel occlusion (RVO)] but did not include the

Table 1 Baseline demographics of patients who received intravitreal dexamethasone versus intravitreal anti-vascular endothelial growth factors (anti-VEGF)

Variables	Before PSM			After PSM		
	Dexamethasone (n = 137)	Anti-VEGF (n = 10,345)	STD	Dexamethasone (n = 131)	Anti-VEGF (n = 393)	STD
Male	65 (47.4)	5706 (55.2)	−0.15	63 (48.1)	180 (45.8)	0.05
Age, years	59.2 ± 16.1	63.0 ± 13.5	−0.25	60.2 ± 15.5	60.1 ± 14.1	< 0.01
Age ≥ 65 years	55 (40.1)	4642 (44.9)	−0.10	55 (42.0)	148 (37.7)	0.09
BMI, kg/m^2	25.0 ± 4.0	25.3 ± 4.0	−0.06	25.4 ± 2.7	25.4 ± 3.5	0.01
Comorbidity						
Hypertension	42 (30.7)	3322 (32.1)	−0.03	40 (30.5)	132 (33.6)	−0.07
Diabetes mellitus	64 (46.7)	4983 (48.2)	−0.03	61 (46.6)	203 (51.7)	−0.10
Dyslipidemia	32 (23.4)	2323 (22.5)	0.02	31 (23.7)	96 (24.4)	−0.02
Heart failure	4 (2.9)	169 (1.6)	0.09	3 (2.3)	10 (2.5)	−0.02
Ischemic heart disease	14 (10.2)	916 (8.9)	0.05	13 (9.9)	50 (12.7)	−0.09
Ischemic stroke	4 (2.9)	338 (3.3)	−0.02	4 (3.1)	15 (3.8)	−0.04
Chronic kidney disease	23 (16.8)	1838 (17.8)	−0.03	21 (16.0)	74 (18.8)	−0.07
Chronic obstructive pulmonary disease	8 (5.8)	640 (6.2)	−0.01	7 (5.3)	29 (7.4)	−0.08
Obstructive sleep apnea	5 (3.6)	277 (2.7)	0.06	5 (3.8)	13 (3.3)	0.03
Charlson Comorbidity Index score	1.9 ± 2.3	1.6 ± 2.0	0.14	1.9 ± 2.3	2.1 ± 2.2	−0.09
Antihypertensive medications						
ACEi/ARB	17 (12.4)	1501 (14.5)	−0.06	17 (13.0)	51 (13.0)	< 0.01
Beta-blockers	15 (10.9)	1016 (9.8)	0.04	14 (10.7)	50 (12.7)	−0.06
Calcium channel blockers	19 (13.9)	1019 (9.9)	0.12	17 (13.0)	52 (13.2)	−0.01
Antihyperglycemic medications						
OHAs	36 (26.3)	2313 (22.4)	0.09	35 (26.7)	112 (28.5)	−0.04
Insulin	13 (9.5)	1173 (11.3)	−0.06	12 (9.2)	41 (10.4)	−0.04
Other medications						
Antiplatelets	18 (13.1)	1220 (11.8)	0.04	18 (13.7)	67 (17.0)	−0.09
Anticoagulants	3 (2.2)	119 (1.2)	0.08	2 (1.5)	5 (1.3)	0.02
Statins	24 (17.5)	1372 (13.3)	0.12	23 (17.6)	75 (19.1)	−0.04
Systemic biomarkers						
SBP, mmHg	137.9 ± 21.4	141.8 ± 22.4	−0.17	140.4 ± 14.1	139.6 ± 15.1	0.05
DBP, mmHg	77.4 ± 10.5	77.8 ± 13.2	−0.04	78.9 ± 7.6	78.7 ± 9.6	0.03

Table 1 continued

Variables	Before PSM			After PSM		
	Dexamethasone (n = 137)	Anti-VEGF (n = 10,345)	STD	Dexamethasone (n = 131)	Anti-VEGF (n = 393)	STD
HbA1c, %	7.2 ± 1.3	7.4 ± 1.8	−0.16	7.4 ± 1.0	7.4 ± 1.3	−0.01
LDL, mg/dL	70.3 ± 37.5	81.9 ± 55.5	−0.25	81.9 ± 22.0	82.2 ± 31.4	−0.01
eGFR, mL/min/1.73 m^2	84.1 ± 36.6	72.5 ± 36.4	0.32	82.6 ± 35.2	77.0 ± 37.8	0.15
ALT, U/L	22.0 ± 12.1	25.1 ± 24.8	−0.16	24.3 ± 8.2	25.0 ± 12.5	−0.06
Indication of IVI						
Age-related macular degeneration	33 (24.1)	4583 (44.3)	−0.44	33 (25.2)	87 (22.1)	0.07
Diabetic retinopathy	47 (34.3)	3585 (34.7)	−0.01	45 (34.4)	141 (35.9)	−0.03
Diabetic macular edema	44 (32.1)	3044 (29.4)	0.06	41 (31.3)	125 (31.8)	−0.01
Retinal vessel occlusion	17 (12.4)	1031 (10.0)	0.08	17 (13.0)	51 (13.0)	< 0.01
Uveitis*	52 (35.1)	172 (1.4)	0.97	48 (33.8)	34 (7.3)	0.70
Ocular history						
Cataract	69 (50.4)	3908 (37.8)	0.26	66 (50.4)	200 (50.9)	−0.01
Use of antiglaucomatous medication	20 (14.6)	324 (3.1)	0.41	16 (12.2)	44 (11.2)	0.03
Vitreous hemorrhage	11 (8.0)	1393 (13.5)	−0.18	11 (8.4)	37 (9.4)	−0.04
Retinal laser	36 (26.3)	2223 (21.5)	0.11	35 (26.7)	104 (26.5)	0.01
Vitrectomy	13 (9.5)	419 (4.1)	0.22	12 (9.2)	38 (9.7)	−0.02
Number of ophthalmology OPD visits at the last 1 year	5.9 ± 4.8	2.7 ± 2.9	0.79	5.6 ± 4.5	5.3 ± 5.1	0.05
Number of IVIs during 1-year follow-up*	2.2 ± 1.7	4.6 ± 4.9	−0.66	2.3 ± 1.7	3.9 ± 3.7	−0.57

Data are presented as frequency (percentage), median (25th percentile, 75th percentile), or mean ± standard deviation
ACEi angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *ALT* alanine amino transferase, *BMI* body mass index, *HbA1c* glycated hemoglobin, *IVI* intravitreal injection, *LDL* low-density lipoprotein cholesterol, *eGFR* estimated glomerular filtration rate, *OHA* oral hypoglycemic agent, *OPD* outpatient department, *PSM* propensity score matching, *STD* standardized difference
*Not included in the calculation of propensity score

number of injections. Each patient who received intravitreal dexamethasone was matched with three patients who used intravitreal anti-VEGFs according to the study index date. A nearest-neighbor algorithm with a caliper of 0.2 times the standard deviation of the logit of the propensity score was used to conduct the matching process. Standardized difference (STD) was calculated to assess the difference between the two groups. An absolute STD value of < 0.2 was considered to represent a nonsubstantial difference.

The incidence of clinical events is expressed herein as the number of events per 100

person–years. The risk of fatal clinical events, including cardiovascular death and all-cause death, was compared using a Cox proportional hazard model. The incidence of other clinical events was compared using the Fine–Gray subdistribution hazard model. The study drugs were the only explanatory variable in the survival analyses. Patients with IVI indications of DME or RVO were selected and the PSM and the above-mentioned analyses were performed. The number of patients with RVO in the intravitreal dexamethasone group was only 17; therefore, we combined the RVO and DME indications.

The changes in systemic biomarkers from baseline to the 12-month time point after therapy were compared using a linear mixed model in which the intercept and slope were set as random effects. A two-sided *P*-value of < 0.05 was considered statistically significant. All analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

RESULTS

Baseline Characteristics

We identified 12,908 patients who received either intravitreal dexamethasone or intravitreal anti-VEGF medications between January 1 2014 and December 31 2019 (Fig. 1). After applying the exclusion criteria, we enrolled 137 patients who received intravitreal dexamethasone and 10,345 patients who received intravitreal anti-VEGFs (Table 1). Before PSM, the proportion of male patients in the dexamethasone group was slightly lower than that in the anti-VEGF group (47.4% versus 55.2%, STD −0.15). Moreover, the mean age in the dexamethasone group was lower than that in the anti-VEGF group (59.2 ± 16.1 versus 63.0 ± 13.5 years, STD −0.25). Both groups had comparable rates of systemic comorbidities and Charlson Comorbidity Index scores. Concerning medications, comparable proportions of the patients in both groups received antihypertensive, antihyperglycemic, and other drugs. Furthermore, regarding systemic biomarkers, both groups exhibited comparable body mass index (BMI), SBP, DBP, HbA1c, eGFR, and ALT levels; however, the dexamethasone group exhibited lower LDL (70.3 ± 37.5 versus 81.9 ± 55.5 mg/dL, STD −0.25) and higher eGFR (50.4 versus 37.8 mL/min/1.73 m^2, STD 0.32) levels. Regarding ocular history, the dexamethasone group had a higher prevalence of antiglaucomatous medication use (14.6% versus 3.1%, STD 0.41), cataracts (50.4% versus 37.8%, STD 0.26), uveitis (35.1% versus 1.4%, STD 0.41), and vitrectomy (9.5% versus 4.1%, STD 0.22), but had a lower prevalence of any AMD (24.1% versus 44.3%, STD −0.44) than did the anti-VEGF group. Additionally, the dexamethasone group recorded a higher number of ophthalmology OPD visits over the preceding year (5.9 ± 4.8 versus 2.7 ± 2.9, STD 0.79) but a lower number of IVIs (2.2 ± 1.7 versus 4.6 ± 4.9, STD −0.66) than did the anti-VEGF group. All covariates became comparable after PSM, and all absolute STD values were < 0.2 between the two groups.

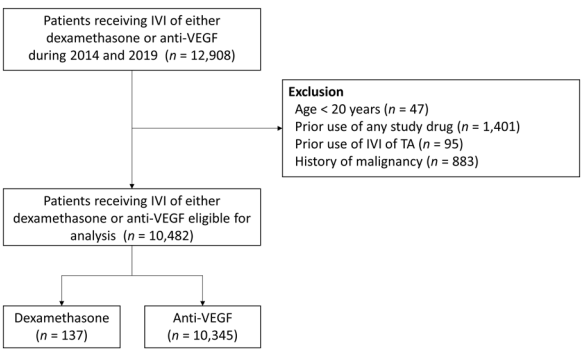


Fig. 1 Patient selection flowchart. *Anti-VEGF* anti-vascular endothelial growth factor agent, *IVI* intravitreal injection, *TA* triamcinolone acetonide

Clinical Events of Primary Interest

The systemic outcomes observed for the dexamethasone and anti-VEGF groups are listed in Table 2. The two groups had comparable incidence rates of MACEs [hazard ratio (HR) 1.57, 95% confidence interval (CI) 0.29–8.55], heart failure [subdistribution HR (SHR) 0.62, 95% CI 0.07–5.33], major bleeding (SHR 0.23, 95% CI 0.03–1.77), and intracranial hemorrhage (SHR

Table 2 Systemic outcomes for intravitreal dexamethasone versus intravitreal anti-vascular endothelial growth factors (anti-VEGF) after propensity score matching during 1-year follow-up

Outcome	Dexamethasone	Anti-VEGF	HR or SHR (95% CI)	*P*-value
Major adverse cardiac event	2.04 (−0.79 to 4.87)	1.29 (0.03 to 2.56)	1.57 (0.29 to 8.55)	0.603
Myocardial infarction	0.00 (0.00 to 0.00)	0.36 (−0.35 to 1.08)	NA	NA
Ischemic stroke	0.00 (0.00 to 0.00)	0.36 (−0.35 to 1.08)	NA	NA
Cardiovascular death	2.04 (−0.79 to 4.86)	0.64 (−0.25 to 1.54)	3.17 (0.44 to 22.65)	0.250
Heart failure	1.12 (−1.08 to 3.32)	1.84 (0.23 to 3.45)	0.62 (0.07 to 5.33)	0.659
Thromboembolism events	0.00 (0.00 to 0.00)	0.73 (−0.28 to 1.74)	NA	NA
Bleeding events				
Major bleeding	1.12 (−1.08 to 3.32)	4.88 (2.23 to 7.53)	0.23 (0.03 to 1.77)	0.158
Gastrointestinal bleeding	0.00 (0.00 to 0.00)	0.73 (−0.28 to 1.74)	NA	NA
Intracranial hemorrhage	1.12 (−1.08 to 3.32)	0.36 (−0.35 to 1.08)	3.05 (0.19 to 48.74)	0.430
All-cause admission	16.7 (8.0 to 25.5)	23.1 (17.1 to 29.2)	0.73 (0.41 to 1.30)	0.286
All-cause death	2.04 (−0.79 to 4.86)	0.97 (−0.13 to 2.06)	2.11 (0.35 to 12.71)	0.415
Overall complications*	17.9 (8.9 to 27.0)	23.9 (17.8 to 30.1)	0.76 (0.43 to 1.34)	0.342

Data are presented as number of events per 100 person–years with 95% CIs

HR hazard ratio, *SHR* subdistribution hazard ratio, *CI* confidence interval, *NA* not applicable

*Indicates anyone of major adverse cardiac event, heart failure, thromboembolism events, bleeding events, all-cause admission, or all-cause death

3.05, 95% CI 0.19–48.74). The two groups also had comparable incidence rates of all-cause hospital admission (SHR 0.73, 95% CI 0.41–1.30) and all-cause death (HR 2.11, 95% CI 0.35–12.71). In addition, both groups presented comparable rates of overall complications (HR 0.76, 95% CI 0.43–1.34). The cumulative event rates are shown in Fig. 2. During the follow-up period, no myocardial infarction, ischemic stroke, thromboembolic events, or gastrointestinal bleeding was detected in the dexamethasone group. Additional analysis of data from the follow-up to the end of the study period consistently showed that the two groups were comparable in the incidence of SAEs (Supplementary Table 2). Subgroup analysis of the patients with DME or RVO consistently showed that the dexamethasone and anti-VEGF groups were comparable in the incidence of SAEs (Supplementary Table 4).

Systemic Biomarkers

The longitudinal changes in systemic biomarkers from baseline to 12 months after therapy in the dexamethasone and anti-VEGF groups are detailed in Supplementary Table 1. As illustrated in Fig. 3, the SBP, DBP, HbA1c, LDL, and ALT levels remained stable during the follow-up period. The changes in SBP (*P* for interaction = 0.869), DBP (*P* for interaction = 0.854), HbA1c (*P* for interaction = 0.513), LDL (*P* for interaction = 0.924), or ALT (*P* for interaction = 0.308) from baseline to 12 months after therapy did not differ significantly between the two groups. Moreover, the eGFR levels persistently declined in both groups, but the changes from baseline to 12 months after therapy did not differ significantly between the two groups (*P* for interaction = 0.160).

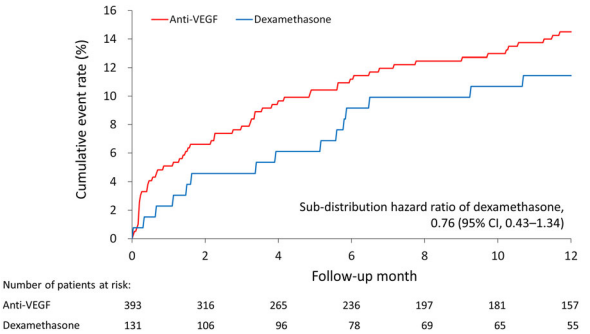


Fig. 2 Cumulative event rate of overall complications for patients receiving intravitreal dexamethasone versus intravitreal anti-VEGFs in the propensity-score-matched cohort during 1-year follow-up. *Anti-VEGF* anti-vascular endothelial growth factor agent, *CI* confidence interval

Clinical Events of Secondary Interest

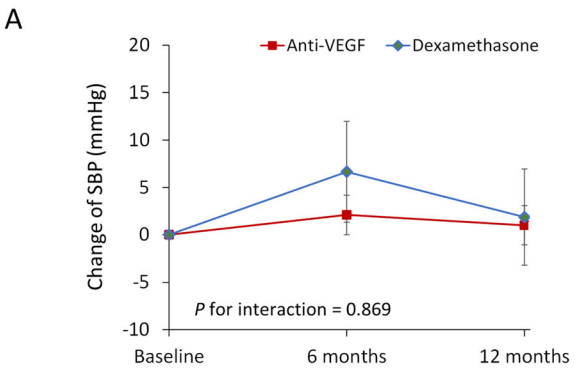
The ocular outcomes of intravitreal dexamethasone and anti-VEGFs in the patients are listed in Table 3. The results revealed that the dexamethasone group had increased use of antiglaucomatous medication (SHR 3.05, 95% CI 1.85–5.01). However, no glaucoma surgery was performed in the dexamethasone group. Additionally, the rates of cataract surgery (SHR 1.28, 95% CI 0.63–2.61) and vitrectomy (SHR 0.43, 95% CI 0.17–1.09) did not differ significantly between the two groups. Additional analysis of data from the follow-up to the end of the study period consistently showed that the dexamethasone group had a higher risk of use of antiglaucomatous medication but was comparable to the anti-VEGF group in the incidence of glaucoma surgery, cataract surgery, and vitrectomy (Supplementary Table 3). Subgroup analysis of patients with DME or RVO consistently showed that the dexamethasone group had a higher risk of use of antiglaucomatous medication but was comparable to the anti-VEGF group in the incidence of glaucoma surgery, cataract surgery, and vitrectomy (Supplementary Table 5).

DISCUSSION

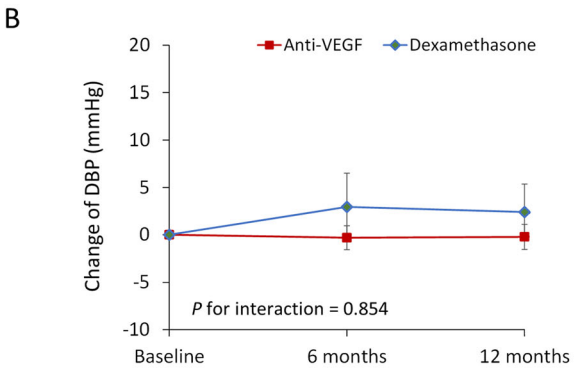
Intravitreal dexamethasone and anti-VEGF medications have revolutionized the management of retinal diseases. Although the safety profiles of intravitreal agents are considered favorable to the eye, few studies have compared the SAEs associated with various intravitreal agents. The present study compared the risks of SAEs in patients who received intravitreal dexamethasone with those in patients who received anti-VEGFs. Our systemic outcomes suggest that both groups had comparable incidence rates of MACEs, heart failure, bleeding events, all-cause admission, and all-cause death. We noted no significant differences in SBP, DBP, HbA1c, LDL, eGFR, or ALT levels between these two groups until the end of follow-up.

According to our review of the literature, most comparative RCTs have revealed similar incidence rates of SAEs between intravitreal dexamethasone and anti-VEGFs [20, 26]. For example, a systemic review and meta-analysis of RCTs in patients with DME observed comparable risks of total SAEs in the dexamethasone and anti-VEGF groups [26]. However, RCTs usually exclude patients with high risks of SAEs, which may limit the generalizability of their safety assessments. Observational studies in clinical practice are still limited. Only one retrospective cohort study reported comparable risks of cerebrovascular disease, myocardial infarction, major bleeding, and all-cause hospitalization between intravitreal triamcinolone and anti-VEGF groups [31]. Nonetheless, the small cohort in that study was insufficient to identify meaningful differences in rare SAEs.

In the present study, both the dexamethasone and anti-VEGF groups demonstrated low risks of SAEs, which is consistent with the findings of previous studies. Two RCTs in patients with macular edema secondary to RVO showed low and comparable incidence of serious adverse event between intravitreal dexamethasone and placebo groups [32, 33]. A systematic review and meta-analysis of 74 RCTs revealed that intravitreal bevacizumab, ranibizumab, and aflibercept groups shared similar risk of MACEs and total mortality with control



Available number			
Dexamethasone	56	35	30
Anti-VEGF	202	127	93



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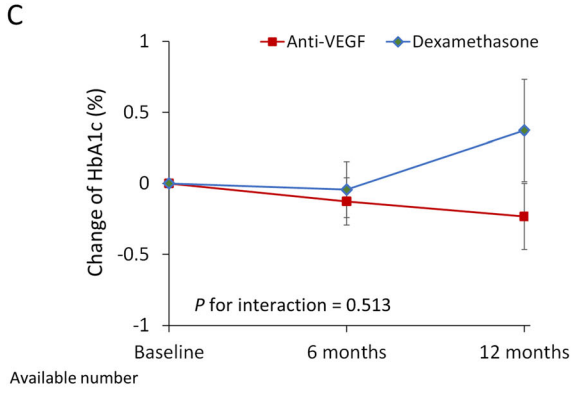
Anti-VEGF	202	127	93



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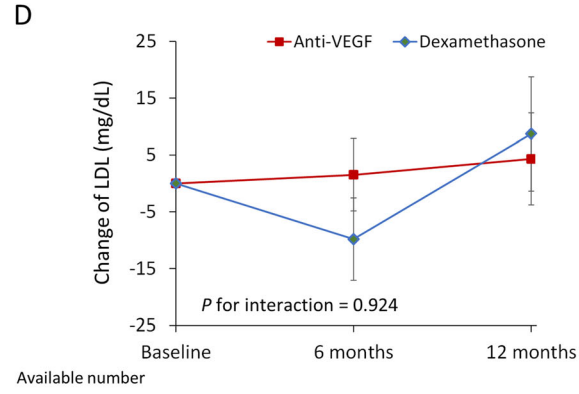
Dexamethasone	54	23	18
Anti-VEGF	180	102	76



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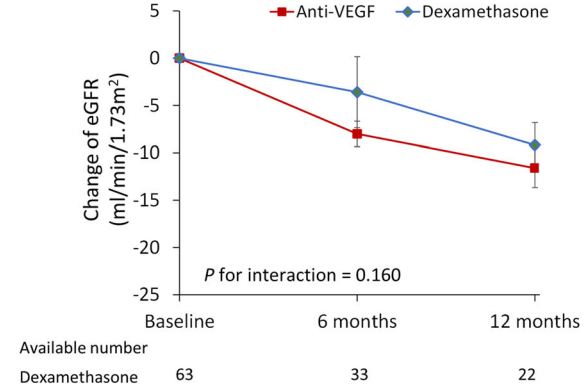
Dexamethasone	35	21	18
Anti-VEGF	142	88	71



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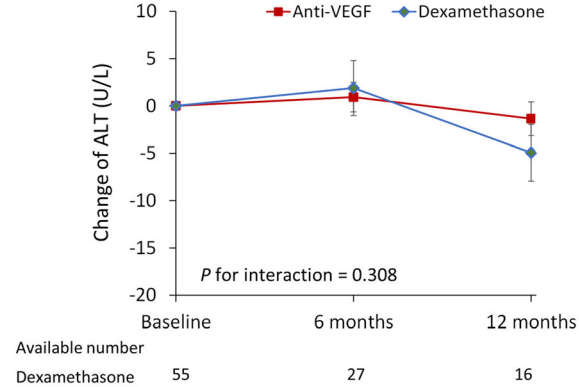
Dexamethasone	63	33	22
Anti-VEGF	191	108	83



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Dexamethasone	55	27	16
Anti-VEGF	161	93	67

◀**Fig. 3** Longitudinal changes in **A** SBP, **B** DBP, **C** HbA1c, **D** LDL, **E** eGFR, and **F** ALT levels in patients who received intravitreal dexamethasone versus those who received intravitreal anti-VEGFs in the propensity-score-matched cohort during 1-year follow-up. *ALT* alanine aminotransferase, *anti-VEGF* anti-vascular endothelial growth factor agent, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *LDL* low-density lipoprotein, *SBP* systolic blood pressure

groups, including sham, no treatment, or non-anti-VEGF standard of care, respectively [22]. The present study observed that the levels of systemic biomarkers remained unchanged in both the dexamethasone and anti-VEGF groups, which is also consistent with the findings of previous studies. A retrospective study revealed no significant difference in HbA1c or creatinine levels before and after intravitreal dexamethasone therapy [34]. Additionally, a retrospective cohort study demonstrated no significant difference in eGFR levels before and after intravitreal bevacizumab, ranibizumab, and aflibercept therapy [35]. Intravitreal agents were hypothesized to induce SAEs through systemic diffusion [8]. However, the dose of intravitreal agents is considerably lower than that of systemic agents [12]. Because of the protective effect of the blood–retinal barrier, the concentrations of intravitreal agents are too low to trigger SAEs or affect systemic biomarkers [8]. Additional studies are necessary to determine the pharmacokinetics and pharmacodynamics of intravitreal dexamethasone and anti-VEGFs.

Regarding our secondary outcomes, we compared the incidence of ocular adverse events between the dexamethasone and anti-VEGF groups. Previous studies have reported that patients who received intravitreal dexamethasone had higher risks of intraocular pressure (IOP) elevation and cataracts than did those who received intravitreal anti-VEGFs [20, 26]. Our study revealed that the dexamethasone group had a higher prevalence of antiglaucomatous medication use but did not require glaucoma surgery, suggesting that most of the patients responded well to antiglaucomatous medication and required no further therapy despite IOP elevation. However, comparable rates of cataracts were observed between the dexamethasone and anti-VEGF groups, a finding that is inconsistent with those of previous studies. The 1-year follow-up period in this study may be too short for cataract development; hence, the discrepancy in cataract formation could be due to the insufficient follow-up period. Intravitreal dexamethasone and anti-VEGFs were thus considered to have good ocular safety profiles within the 1-year follow-up period.

According to our review of the literature, this is the first study to compare SAEs between intravitreal dexamethasone and anti-VEGFs by using a multi-institutional database in Taiwan. This study has several strengths. First, the changes in systemic biomarkers during the follow-up period provided extra information regarding disease status. Second, the active-

Table 3 Ocular outcomes for intravitreal dexamethasone versus intravitreal anti-vascular endothelial growth factors after propensity score matching during 1-year follow-up

Outcome	Dexamethasone	Anti-VEGF	SHR (95% CI)	*P*-value
Use of antiglaucomatous medications	37.2 (23.2–51.2)	11.6 (7.4–15.7)	3.05 (1.85–5.01)	< 0.001
Glaucoma surgery	0.00 (0.00–0.00)	2.59 (0.67–4.51)	NA	NA
Cataract surgery	12.9 (5.3–20.5)	10.0 (6.1–13.8)	1.28 (0.63–2.61)	0.495
Vitrectomy	5.8 (0.7–10.8)	13.5 (8.9–18.0)	0.43 (0.17–1.09)	0.074

Data are presented as number of events per 100 person–years with 95% CIs
SHR subdistribution hazard ratio, *CI* confidence interval, *NA* not applicable

comparator and new-user design minimized bias. After adjustment through PSM, all covariates were well balanced. Third, the sufficient follow-up provided powerful evidence for our outcomes. Our follow-up period is considerably longer than that of the only real-world study comparing SAEs between intravitreal dexamethasone and anti-VEGFs (365 versus 147 days) [31]. Nevertheless, our study also has some limitations. First, although we systematically balanced multiple variables by using PSM, the confounding effects could not be eliminated entirely due to the retrospective nature of this study. Second, the population from the CGRD primarily comprised patients of Asian heritage. Therefore, the SAEs of intravitreal dexamethasone and anti-VEGFs require further investigation in other populations. Third, patients who experienced SAEs at institutions other than CGMH were not recorded in the database; thus, the rates of those SAEs could have been underestimated. Nevertheless, this issue would occur nondifferentially across both groups, and the relative effect estimates should remain unbiased. Fourth, data from the CGRD did not contain IOP values; hence, we identified IOP elevation only through examining the use of antiglaucomatous medications. Additionally, ocular adverse events were detected on the basis of the individual but not the laterality of the eye. Fifth, when more than one indication (replied on diagnosis) was identified in the same patient, the exact indication for intravitreal injection could not be specified due to the nature of retrospective database design. However, the baseline demographics became well balanced between the two groups after PSM. Sixth, the population of dexamethasone users with one indication was insufficient for effective statistical analysis. Therefore, the patients with DME or RVO were clustered for subgroup analysis. Finally, the relatively low population in the dexamethasone group compared with the anti-VEGF group in this study may have affected the statistical significance of our findings.

CONCLUSION

Intravitreal dexamethasone and anti-VEGF medications were observed to have similar safety profiles in our clinical study. Both the dexamethasone and anti-VEGF groups exhibited comparable rates of MACEs, heart failure, bleeding events, all-cause admission, and all-cause death. Additionally, we observed no significant differences in long-term changes in SBP, DBP, HbA1c, LDL, eGFR, or ALT levels between the dexamethasone and anti-VEGF groups. Accordingly, these efficacious and well-tolerated agents can be safely prescribed to patients with ocular diseases.

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Author Contributions. Tzu-Yi Lin, Yih-Shiou Hwang, and Eugene Yu-Chuan Kang designed the study. Yih-Shiou Hwang and Eugene Yu-Chuan Kang collected the data. Yi-Ting Hsieh, Lee-Jen Chen, and Kuan-Jen Chen analyzed the data. Tzu-Yi Lin and Eugene Yu-Chuan Kang drafted the manuscript. Eugene Yu-Chuan Kang and Sunir J. Garg revised the manuscript. Yih-Shiou Hwang, Wei-Chi Wu, and Chi-Chun Lai performed a critical review. All authors read and approved the final manuscript.

Disclosures. All named authors declare that they have no competing interests.

Compliance with Ethics Guidelines. This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. This study was approved by the Chang Gung Medical Foundation Institutional Review Board (IRB No. 202200606B1). Written informed consent was waived due to the deidentification and encryption of patient data.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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