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ORIGINAL RESEARCH

Real-World Safety Outcomes of Intravitreal Ranibizumab Biosimilar (Razumab) Therapy for Chorioretinal Diseases

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ABSTRACT

Introduction: To assess the safety profile of the intravitreal ranibizumab biosimilar molecule, Razumab® (Intas Pharmaceuticals, Ahmedabad, India) in chorioretinal disorders under real-world conditions.

Methods: This was a multicenter, retrospective chart review which included patients from 15 centers receiving intravitreal Razumab (IVRz) injections from 2016 to 2020. Patient demographics, ocular examination data, and detailed safety information regarding serious adverse events (SAE) or serious adverse drug reactions (sADR), and non-serious AEs (nsAE) or non-serious ADRs (nsADR) occurring within 1 month of IVRz injections were compiled.

Results: A total of 6404 eyes of 6404 patients received 9406 IVRz injections [mean (± SD) = 1.49 (± 0.63)] during 4.25 years. Adverse events were reported after 1978 injections (21.03%): 64.16% nsAE, 32.96% nsADR, 2.37% sADR, and 0.51% SAE. The most frequent adverse events were subconjunctival hemorrhage (8.2% of total injections), transient

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blurring of vision (6.5% of total injections), and mild ocular pain (5.27% of total injections). Serious ocular (31 cases with retinal pigment epithelial tears [0.33%], two cases of non-infectious vitritis [0.02%], and one case of endophthalmitis [0.01%]) and systemic (seven patients with non-fatal myocardial infarction [0.12%] and six patients with non-fatal cerebrovascular accident [0.09%]) adverse events were infrequent.

Conclusion: The study reports the largest pooled safety data on IVRz use in a real-world scenario. The results did not raise any new ocular or systemic safety concerns for the biosimilar agent, with the incidence and spectrum of adverse reactions similar to those reported with other anti-vascular endothelial growth factor (anti-VEGF) drugs. The real-world evidence suggests that IVRz is a safe anti-VEGF agent in the management of chorioretinal disorders.

Keywords: Razumab; Biosimilars; Ranibizumab; Anti-vascular endothelial growth factor; Safety profile

Key Summary Points

Why carry out this study?

Biosimilars of anti-vascular endothelial growth factor (anti-VEGF) drugs are an appealing therapeutic alternative to the parent biologic since they have the potential to reduce the cumulative cost of treatment in various chorioretinal disorders.

Although the Indian regulatory approved ranibizumab biosimilar Razumab® (Intas Pharmaceuticals, Ahmedabad, India) has demonstrated good efficacy and safety based on phase III studies, the limited number of patients treated in a controlled environment may not truly reflect the delivery settings and the population diversities in real-world scenarios.

We performed a pooled safety data analysis of 9406 intravitreal Razumab (IVRz) injections in 6404 eyes of 6404 patients with treatable chorioretinal vascular diseases.

What was learned from the study?

Adverse events (AEs) were noted with 21.03% of injections, although 97.12% of them were non-serious. Serious ocular and systemic events were infrequent (57 events/9406 injections; 0.61%), including retinal pigment epithelial tears (33 eyes; 0.33%), non-infectious vitritis (2 eyes; 0.02%), endophthalmitis (1 eye; 0.01%), non-fatal myocardial infarction (seven patients; 0.12%), and non-fatal cerebrovascular accident (six patients; 0.09%).

In a real-world setting, intravitreal Razumab therapy has an acceptable ocular and systemic safety profile in the management of chorioretinal disorders.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14333870.

INTRODUCTION

Chorioretinal vascular diseases, including age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO), are among the leading causes of vision impairment and blindness throughout the world [1, 2]. Aging of the population and epidemic-like growth in the number of patients with metabolic syndrome are projected to increase the global prevalence of AMD from 170 million in 2014 to 288 million by 2040 [3] and of diabetes mellitus from 415 million in 2015 to 642 million by 2040 [4]. In more severe cases,

the vision loss from these maculopathies significantly impacts patients' quality of life and general well-being [5, 6]. The increasing social and economic costs associated with these diseases have public health officials increasingly concerned [4, 7].

The management of these disorders over the past 16 years has been revolutionized by the rapid, widespread adoption of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy [8]. Four drugs (pegaptanib sodium (Macugen®, Eyetech/OSI Pharmaceuticals, New York, NY, USA), ranibizumab (Lucentis®; Genentech, South San Francisco, CA/Roche, Basel, Switzerland), aflibercept (Eylea®, Regeneron, Tarrytown, NY), and brolucizumab (Beovu®; Novartis, Basel, Switzerland)) [9–11] have been approved by the US Food and Drug Administration (FDA) for intraocular use while bevacizumab (Avastin®; Genentech, South San Francisco, CA/Roche, Basel, Switzerland) is used off-label [12].

To optimally treat retinal disorders these drugs must be injected repeatedly over many years but the high cost of a treatment regimen with a branded drug is prohibitive for many patients. This underscores the need for a widely available, economical, and effective anti-VEGF drug with an acceptable safety profile. Bevacizumab meets most of these criteria but its off-label use has not been sanctioned by regulatory agencies in some parts of the world and the need for compounding increases the risk of infection.

Biosimilar drugs that are structurally and functionally similar to approved biological agents could be an important advance in the management of retinal disorders [13]. Razumab® (Intas Pharmaceuticals, Ahmedabad, India), the first biosimilar of ranibizumab, was approved by the Drug Controller General of India (DGCI) in 2015 after a phase 3 trial demonstrated its efficacy and safety in 103 eyes with nAMD and 160 eyes with macular edema due to RVO [14, 15].

Intravitreal anti-VEGF drugs have been associated with both ocular (from subconjunctival hemorrhage to vision-threatening endophthalmitis, vitreous hemorrhage, and retinal detachments) and systemic (myocardial infarctions (MI), strokes, systemic thromboembolic episodes (TEEs), and systemic arterial hypertension) adverse events [16, 17]. The phase 3 RE-ENACT trial failed to identify any new safety concerns with intravitreal Razumab (IVRz) injections but sporadic cases of sterile endophthalmitis with early production batches [14, 15, 18] forced the developer to modify the manufacturing process with no subsequent incidents of sterile endophthalmitis seen after January 2019.

The data from RE-ENACT suggests that IVRz is safe but the relatively small number of treated eyes (263) may not mirror outcomes from more widespread real-world use. The present study reports the ocular and systemic safety profiles from the real-world use of IVRz in 15 tertiary care centers in India over a period of 5 years (2016–2020).

METHODS

This multicenter, collaborative, retrospective chart review included patients from 15 tertiary eye care centers in India. Eligible patients received IVRz injections between January 2016 and March 2020 and were followed for a minimum of 1 month. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Master Ethical Committee of Disha Eye Hospitals in Kolkata and by the institutional review board at each center. Written informed consent for treatment and data collection was obtained from each patient.

Patient Recruitment and Treatment

Patients with treatable chorioretinal vascular diseases (nAMD, DME, macular edema due to RVO) were advised to receive intravitreal anti-VEGF therapy. Treatment with any of the available anti-VEGF drugs was offered and eligible patients freely chose to receive IVRz (0.5 mg in 0.05 mL). As per our study protocol, in cases where the patient had a bilateral disease, only *one* eye of the patient was offered treatment with the biosimilar drug (Razumab).

The treatment regimen [pro re nata (PRN) from baseline/three monthly doses followed by PRN/treat-and-extend (TnE) from baseline/three monthly doses followed by TnE] was based on the retinal physician's discretion depending on the underlying diagnosis and the patient profile. All injections were performed in an operating theater under sterile technique. Povidone-iodine 5% was applied to eyes both immediately before and after each injection, preoperative antibiotic eye drops were not given, but topical moxifloxacin 0.5% was administered postoperatively for 1 week.

Data Collection

After each injection, the patients were followed up on the second day, at 1 week and at 1 month. Additionally, the patients were advised to follow up immediately at the center in case of occurrence of any ocular or systemic adverse event. At all visits, a detailed history was taken by the treating physician regarding the occurrence of any ocular and systemic adverse event. Additionally, a thorough clinical examination including best-corrected visual acuity (BCVA) assessment using the Snellen's visual acuity chart, intraocular pressure (IOP) measurement by Goldmann applanation tonometer, anterior segment evaluation using slit-lamp biomicroscopy and fundus examination with both slit-lamp biomicroscopy (+ 90 D lens) and indirect ophthalmoscopy (+ 20 D lens) was undertaken by the retina specialist. Additionally, spectral-domain optical coherence tomography (SD-OCT) was performed at the 1-month visit. The protocol for the follow-up visits and clinical examination was uniformly adhered to at each of the 15 centers. Demographic and clinical data including age, primary diagnosis, systemic history, BCVA, and IOP at baseline and final visits, and any complications occurring within 1 month of the injection(s) were extracted from the electronic medical database.

Outcome Measures

Adverse events (AEs) and adverse drug reactions (ADRs) were identified in the medical records. On the basis of the Harmonised Tripartite Guidelines on Clinical Safety Data Management (E2A) by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), an AE is defined as "Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment." Similarly, "all noxious and unintended responses to a medicinal product related to any dose should be considered ADR" whereby "The phrase 'responses to a medicinal product' means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out" [19].

The AEs and ADRs were subclassified as serious AEs (SAE) or serious ADRs (sADR), and non-serious AEs (nsAE) or non-serious ADRs (nsADR). A SAE or sADR was defined as any event that occurred at any dose that resulted in death, a life-threatening AE, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Events that did not fulfill these criteria were labeled as nsAE or nsADR. All AEs were reported by the treating vitreoretinal specialist and categorized on the basis of his/her clinical judgment.

Statistical Analysis

Data was analyzed using Radical NewCharts Horizon v0.1 and independently verified using scipy and numpy. Continuous variables were characterized with mean and standard deviation (SD), and categorical variables were characterized with frequencies and percentages. The rate of AEs was expressed as a fraction with the total number of injections serving as the denominator.

RESULTS

A total of 31,645 intravitreal anti-VEGF injections were performed during the 4.25-year study

Table 1 Demographic characteristics of the study population

Characteristic	Number of patients (total 6404)
Age (years)	
Mean (± SD)	55.51 (10.11)
Gender	
Male	3395 (53.01%)
Female	3009 (46.99%)
Total number of injections per patient	
Mean (± SD)	1.49 (0.63)

SD standard deviation

Table 2 Lists of indications for intravitreal Ranibizumab biosimilar injections

Ocular pathology	Eyes (%) (total 6404)
DME	2141 (33.43)
BRVO	1689 (26.37)
nAMD	979 (15.29)
Preoperative adjuvant for PDR surgery	693 (10.82)
CRVO	391 (6.11)
Myopic CNVM	134 (2.1)
NVG	26 (0.41)
CSCR	13 (0.2)
Miscellaneous	348 (5.43)

DME diabetic macular edema, *BRVO* branch retinal vein occlusion, *nAMD* neovascular age related macular degeneration, *PDR* proliferative diabetic retinopathy, *CRVO* central retinal vein occlusion, *CNVM* choroidal neovascular membrane, *NVG* neovascular glaucoma, *CSCR* central serous chorioretinopathy

period at the participating centers, including the innovator ranibizumab (Lucentis), biosimilar ranibizumab (Razumab), aflibercept (Eylea), and bevacizumab (Avastin). Of these 31,645 anti-VEGF injections, 9406 IVRz injections were performed in 6404 eyes of 6404 patients [mean (± SD) = 1.49 (± 0.63)] (Table 1). The mean (± SD) age of the patients was 55.51 (10.11) years, and the majority were male (3395; 53.01%). The most common indications for IVRz injections were DME (3040 injections; 32.32%), neovascular AMD (nAMD; 2574 injections; 27.37%), and branch retinal vein occlusion (BRVO; 2195 injections; 23.34%). Table 2 lists the chorioretinal conditions that were treated.

Adverse Events

Adverse events were reported after 1978 (21.03%) IVRz injections; of these, 1269 were nsAE (64.16%), 652 were nsADR (32.96%), 10 were SAE (0.51%), and 47 were sADR (2.37%). Table 3 provides a summary of the adverse events.

nsAEs

Non-serious AEs occurred with 13.49% of the injections, with 772 subconjunctival hemorrhages (8.2% of the total number of injections) and 497 episodes of mild ocular pain (5.27% of the total number of injections) most commonly. These nsAEs resolved with conservative management and without any long-term complications.

nsADR

Non-serious ADRs occurred with 6.93% of the injections, with transient blurring of vision (612 injections; 6.5%), elevated intraocular pressure (31 injections; 0.33%), and mild anterior uveitis (9 injections; 0.1%) being most common. Transient blurring of vision resolved with conservative management in all patients. All eyes with elevated IOP (maximum recorded was 32 mmHg) were managed with topical pressure-lowering medications, with no episodes of vision loss, and none of the eyes required surgical intervention. Mild anterior uveitis resolved in all nine eyes following brief courses of topical corticosteroids.

Table 3 List of ocular and systemic adverse events in patients receiving intravitreal Ranibizumab biosimilar injections

Adverse event	Frequency (%)
Total (number of events/total number of injections [9406])	1978 (21.03)
nsAE (number of events/total number of injections [9406])	
Subconjunctival hemorrhage	772 (8.2)
Mild ocular pain	497 (5.27)
Total	1269 (13.49)
nsADR (number of events/total number of injections [9406])	
Transient blurring of vision	612 (6.5)
Raised IOP	31 (0.33)
Mild anterior uveitis	9 (0.1)
Total	652 (6.93)
SAE (number of events/total number of injections [9406])	
VH	5 (0.05)
Hyphema	4 (0.04)
Lens injury	1 (0.01)
Total	10 (0.1)
sADR (ocular) (number of events/total number of injections [9406])	
RPE tears	31 (0.33)
Non-infectious vitritis	2 (0.02)
Infectious endophthalmitis	1 (0.01)
Total	34 (0.36)
sADR (systemic) (number of events/total number of patients [6404])	
Non-fatal MI	7 (0.12)
Non-fatal CVA	6 (0.09)
Total	13 (0.21)

nsAE non-serious adverse event, *nsADR* non-serious adverse drug reaction, *IOP* intraocular pressure, *SAE* serious adverse event, *VH* vitreous hemorrhage, *sADR* serious adverse drug reaction, *RPE* retinal pigment epithelium, *MI* myocardial infarction, *CVA* cerebrovascular accident

SAE

Serious adverse events occurred after 0.1% of injections. Vitreous hemorrhage occurred in five eyes (0.05%), three of which had proliferative diabetic retinopathy (PDR), while two eyes with nAMD had extension of subretinal hemorrhage into the vitreous. Hyphema occurred in four eyes (0.04%). In each of these eyes, the hemorrhage was believed to be due to underlying ocular disease rather than the drug or the injection. One eye (0.01%) sustained a lens injury during the injection and the resultant cataract was successfully removed.

sADR

Serious ADRs occurred in 47 eyes (0.5%). Two eyes (0.02%) developed non-infectious vitritis that completely resolved after intensive treatment with topical and oral corticosteroids. One eye (0.01%) developed infectious endophthalmitis that was successfully managed with pars plana vitrectomy and intravitreal antibiotics. Retinal pigment epithelial tears occurred in 31 eyes (0.48%).

Non-fatal thromboembolic events occurred in 13 patients (0.2%), all within 1 month of receiving IVRz injections. Seven patients with myocardial infarctions all had underlying diabetes and hypertension, three of them had received injections for DME and four had received injections for nAMD. Six of the seven patients (four with nAMD and two with DME) had previously received two or more intravitreal anti-VEGF injections.

Six patients with cerebrovascular accidents (CVA) all had systemic arterial hypertension and four had diabetes. Indications for anti-VEGF injections in these patients were nAMD (four eyes), DME (one eye), and RVO (one eye). Five of these patients had previously received two or more anti-VEGF injections while one eye with an RVO received only IVRz.

DISCUSSION

In this real-world safety study of the ranibizumab biosimilar Razumab, AEs were seen with 21.03% of injections, but most (1921/1978; 97.12%) were non-serious. Serious AEs were rare (57/9406; 0.61%) with 10 categorized as SAE (0.1%) and 47 (0.51%) as drug-related sADR. Our study shows that adverse events with Razumab are not different than those already described with other anti-VEGF drugs.

Anti-VEGF therapy is widely accepted as standard of care for the management of various chorioretinal disorders, and though ocular and systemic adverse events have been observed, numerous trials have shown that intravitreal therapy has an excellent overall safety profile [16, 17, 20–24]. Nevertheless, treating physicians should be familiar with drug-related AEs, particularly those that are vision- or life-threatening.

The RE-ENACT 2 trials found that Razumab was safe and effective through 48 weeks in patients with nAMD and RVO [25, 26], and though no new safety concerns with Razumab were mentioned, the authors failed to address safety concerns other than IOP changes. There were no significant changes in the mean IOP at any of the visits in RE-ENACT [25, 26] but 31 (0.48%) eyes in our study had transient increases in IOP (greater than 21 mmHg) at 1 month but all were successfully managed with pressure-lowering medications.

IOP increases may occur immediately after anti-VEGF injections (due to an increase in vitreous volume) or after a series of injections (due to impaired aqueous outflow). A meta-analysis showed a statistically significant rise in IOP on the day of the injection followed by a significant decline the next day with no changes at the subsequent visits up to 12 months [27]. A recent report by the American Academy of Ophthalmology (AAO) on the effect of anti-VEGF therapy on IOP and glaucoma also noted a short-term elevation in IOP immediately after the injection followed by a gradual normalization over a week [28]. We did not find immediate IOP changes in our study but since this was a retrospective review the investigators may not have routinely measured IOP immediately after injections and they may have failed to document transient increases.

The AAO report showed mixed results regarding long-term IOP changes—seven studies described a 4–15% incidence of sustained IOP elevation from 9 to 24 months after initiation of therapy, whereas six studies reporting no long-term changes in IOP at 1 to 36 months [28]. Prospective trials reported that 3.5–8.5% of nAMD eyes receiving ranibizumab or bevacizumab may develop a sustained rise in IOP [27–29] and the incidences of sustained IOP greater than 21 mmHg were 8.4%, 3.2%, 4.2%, and 2.7% in the q4wk ranibizumab (Rq4), 2 mg aflibercept every 4 weeks (2q4), 0.5 mg aflibercept every 4 weeks (0.5q4), and 2 mg aflibercept every 8 weeks (after 3 monthly doses; 2q8) groups, respectively in the VIEW 1 & 2 trials [30]. The incidence of IOP elevation in our study was small (0.48%) but since most of these eyes received only single Razumab injections, directly comparing our findings to those from 2-year trials should not be done. An increasing number of eyes in our study are likely to experience sustained elevations in IOP once they have received more injections.

Meta-analyses of clinical trials and real-world data report endophthalmitis rates that range from 0.026% to 0.056% [31, 32], and a comparative analysis of 503,890 anti-VEGF injections found endophthalmitis rates of 0.0039%, 0.0035%, and 0.0035% for bevacizumab, ranibizumab, and aflibercept, respectively [33]. The authors concluded that anti-VEGF drugs should be chosen for efficacy and patient response rather than out of concern for infection [33]. Similar endophthalmitis rates were found between the ranibizumab biosimilar agent SB11 2/350 (0.6%) and ranibizumab 0/354 (0%) but the small sample sizes prevent a meaningful

comparison [34]. Our larger sample size (9406 injections) detected an endophthalmitis rate of 0.01%, which is similar to that with other anti-VEGF drugs.

Non-infectious endophthalmitis, which can be a direct immune response against the molecule itself or a reaction to drug-related impurities, has been described with each of the anti-VEGF drugs. The Fight Retinal Blindness! (FRB!) registry reported non-infectious endophthalmitis rates with bevacizumab (8/9931; 0.081%), ranibizumab (3/54,776; 0.005%), and aflibercept (0/23,425) [35], while a study of 100,588 anti-VEGF injections reported rates of 0.10% (67 cases) for bevacizumab, 0.02% (six cases) for ranibizumab, and 0.16% (13 cases) for aflibercept [36]. Additionally, cases of intraocular inflammation (IOI) are being reported with the use of brolucizumab. The incidence of IOI in the HAWK and HARRIER studies was 4% for brolucizumab as compared to 1% for aflibercept [37]. The American Society of Retinal Specialists (ASRS) had issued an alert in February 2020 after 14 cases of retinal vasculitis, of which 11 were occlusive vasculitis, were reported after use of IVI brolucizumab [38]. We found a non-infectious vitritis rate of 0.02% (2/9406) with Razumab, similar to that reported with other anti-VEGF drugs (0.05–2.9%) [16, 17] and lower than that (0.3%) attributed to SB11 [34]. Biologics are protein derivatives and hence can incite an immune reaction, potentially by producing anti-drug antibodies (ADA) [39]. These ADAs have been demonstrated in the patient's serum after receiving anti-VEGF therapy, probably in response to the systemically absorbed portion of the drug [39]. Although biosimilars are produced by a process of reverse engineering and are very similar to the innovator molecule, they can potentially contain some proteinaceous impurities which can give rise to incidents of IOI. Further studies into this vital aspect of biosimilars are warranted to reduce the incidents of post-injection inflammation.

Systemic safety of intravitreal anti-VEGF drugs remains an unresolved issue since no prospective trials have been sufficiently powered to detect a relationship. Systemic adverse events associated with intravitreal anti-VEGF therapy include systemic arterial hypertension, myocardial infarction, thromboembolic events, and cerebrovascular events such as stroke or transient ischemic attacks [16, 17]. The reported rates of systemic adverse events associated with intravitreal anti-VEGF therapy range from 0.6% to 13% [16, 32, 40]. In the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T trial, ranibizumab was associated with Higher Antiplatelet Trialists' Collaboration (APTC) event rates (12%) as compared to aflibercept (8%) or bevacizumab (5%) over 2 years [41]. At 2 years, the CATT, IVAN, and VIEW studies did not show any significant difference in APTC events between ranibizumab and bevacizumab groups or between aflibercept and ranibizumab groups [42–44]. We noted 13 (0.2%) cases of non-fatal APTC events, including seven cases of MI and six cases of stroke in patients receiving IVRz, but this was with a mean follow-up of just over 1 month per patient. If this incidence were to be extrapolated to 2 years of treatment per patient, an estimate rate of 4.8% would be similar to that seen with longer studies with other anti-VEGF drugs. As with previously published randomized controlled trials of anti-VEGF therapy, our study was insufficiently powered to determine the risks of systemic adverse events [45].

In addition to efficacy and safety, cost-effectiveness is often considered by physicians when selecting an anti-VEGF drug. The high cost of many anti-VEGF treatment regimens limits the number of treatments that many patients can afford and often prevents the achievement of a satisfactory, sustained outcome. For this reason, many physicians choose to use the much less expensive, off-label bevacizumab for their patients [12]. Dozens of intravitreal doses can be prepared from a single-use vial intended for intravenous use but compounding has been associated with contaminated syringes and incidents of multi-patient endophthalmitis. Biosimilar drugs that are approved by regulatory agencies could be effective, safe, and cost-effective alternatives to available therapies. Biosimilars could reduce treatment costs by 25–50% when compared to their parent biologic drugs [13]. Razumab is relatively inexpensive (US $125) compared to Lucentis (Branded Accentrix; US $320), Eylea

(US $760), and Beovu (Branded Pagenax; US $350) in India. Through March 2020, 120,582 Razumab injections had been administered in India. Razumab clinical trials (RE-ENACT study and RE-ENACT 2 study) provided safety and efficacy data for the treatment of nAMD and RVO [14, 15, 25, 26], and as a result, Razumab sales have increased from 2842 vials in 2015 to 49,914 vials in 2019 [46]. The RE-ENACT studies were 12-week phase 3 clinical trials which ascertained the efficacy of Razumab in 103 eyes with nAMD and 160 eyes with RVO [14, 15]. Later, the 48-week RE-ENACT 2 trial showed significant improvement in BCVA, central subfield thickness, intraretinal and subretinal fluid till the final visit in eyes with nAMD [25]. The corresponding RE-ENACT trial for RVO also demonstrated significantly improving the BCVA and reduction in the macular thickness at 48 weeks [26].

The major limitations of the present study are the retrospective design and brief follow-up period. Since results are limited to the data reported in the medical records, under-reporting of adverse events, particularly systemic adverse events, may have occurred. The brief follow-up period (1 month after injections) may have been insufficient to detect adverse events that develop over longer periods of time. We lacked a control group against which a comparative safety analysis might have been performed.

CONCLUSION

Our data from a large cohort (9406 injections) of eyes treated with Razumab suggest that IVRz may be a safe alternative to approved anti-VEGF drugs. Long-term prospective studies with appropriate control groups are needed to validate the ocular and systemic safety of IVRz injections.

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Disclosures. Debdulal Chakraborty, Jay Sheth, Tushar Sinha, Subhendu Boral, Arnab Das, Soumen Mondal, Angshuman Mukherjee declare that they have no conflict of interest related to this work. Outside the submitted work, Michael Stewart reports Institutional Research Support—Kang Hong, Santen; and Consultant—Alkahest, Bayer.

Compliance with Ethics Guidelines. Written informed consent for treatment and data collection was obtained from each patient. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Master Ethics Committee of Disha Eye Hospitals (Regn Number ECR/846/Inst/WB/2016/RR-19: EC-CT-2020-138) in Kolkata and by the institutional review board at each center.

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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