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Original Research Article

Long-term efficacy and safety of Razumab™ (biosimilar ranibizumab) in Indian patients with retinal diseases: results from retrospective REAR RD-2 study

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ABSTRACT

Background: To evaluate risk factors associated with retinal diseases and efficacy and safety of Razumab™ (biosimilar ranibizumab) in the management of retinal diseases in Indian patients with wet age-related macular degeneration (wet AMD), diabetic macular edema (DME), retinal vein occlusion (RVO) and myopic choroidal neovascularization (mCNV).
Methods: In the retrospective, observational REAR RD-2 study, all patients with retinal diseases who were treated with biosimilar ranibizumab were included from multiple Indian sites. The demographic parameters, disease characteristics and treatment details were recorded. Efficacy assessments included improvement in best corrected visual acuity (BCVA), and decrease in central subfield thickness (CSFT), intra-retinal fluid (IRF) and sub-retinal fluid (SRF) from baseline to week 48.
Results: Data of 1422 patients (wet AMD-27.57%; DME-30.7%, RVO-33.47%; mCNV-5.48%), who were treated with biosimilar ranibizumab, was analyzed. The most common age group of patients was 61-70 years (36.6%). The most common ocular risk factor identified was glaucoma (24.90%). A total of 85.72% patients were treatment naïve and 14.28% were previously treated patients. Biosimilar ranibizumab treatment resulted in significant ($p<0.05$) improvements in the mean BCVA and CSFT, and the proportion of patients with IRF and SRF was significantly reduced throughout the treatment. No new safety concerns with biosimilar ranibizumab were observed.
Conclusions: Retinal diseases are more common in the age group of 61-70 years. Glaucoma was the most common ocular risk factor identified for retinal diseases. Long-term treatment with biosimilar ranibizumab was effective and well-tolerated in retinal diseases including wAMD, DME, RVO and mCNV in real-world Indian scenario.

Keywords: Wet AMD, DME, RVO, mCNV

INTRODUCTION

Retinal diseases, are characterized by leakage of fluid, haemorrhage, and fibrous scarring in the retina causing visual impairment.[1] Retinal diseases include wet AMD, DME, RVO, mCNV etc and vascular endothelial growth factor (VEGF) play an important role in their pathogenesis.[2]

Anti-VEGF agents play a crucial role in the treatment of several retinal diseases.[3] Currently approved anti-VEGF therapies in retinal diseases include ranibizumab, aflibercept and brolucizumab.[4] Ranibizumab, a recombinant humanized monoclonal antibody, binds to all biologically active isoforms of VEGF,[5] and has been used extensively for the treatment of wet AMD, DME, RVO and mCNV.[6-9] Intas Pharmaceuticals Ltd., Ahmedabad, India has developed a biosimilar

ranibizumab, Razumab™, to provide an efficacious, safe and cost-effective alternative to the innovator ranibizumab.[10] It has been approved by the Drugs Controller General of India (DCGI) in 2015 for the treatment of wet AMD, RVO, DME, and mCNV. It has been also recently approved by DCGI in 2022 for the treatment of proliferative diabetic retinopathy (PDR) and retinopathy of prematurity (ROP).

Although several prospective, randomized, double-masked, clinical trials have documented the safety and efficacy of various anti-VEGF agents including ranibizumab in the treatment of retinal diseases, real-world observational studies provide strong evidence overcoming the limitations of the restrictive clinical trial designs and well-defined inclusion and exclusion criteria. Documentation of the associated risk factors in retinal diseases aid to decide management approach in these patients. Hence, this current real-world, retrospective, observational, multi-center study was conducted to evaluate the potential risk factors associated with retinal diseases and the efficacy and safety of biosimilar ranibizumab in the management of retinal diseases in Indian patients.

METHODS

Study design

REAR RD-2 (REal world observational study to evaluate the Risk factors in the management of Retinal Diseases-2) was a real-world, retrospective, cross sectional, observational study. The study data was collected between April 2021 and March 2022. The study centers included hospitals, clinics, and health care institutes across India. Patients with retinal diseases and who received treatment with biosimilar ranibizumab were included in the study. Patients with concomitant ophthalmology conditions such as media opacities (dense cataract or corneal opacity etc.), which limited the ability to acquire good images, ocular infection, ocular inflammation, previous vitrectomy, uncontrolled glaucoma etc. were excluded. The data of patients was collected from the medical records by retina specialists at the respective study centers in the predefined REAR RD-2 study data collection form.

Study variables

Patients were selected based on treating retina specialists' discretion, and no additional evaluation or investigations were performed during data capture in this real-world, observational study.

The demographic parameters including the age, gender, history of comorbidities such as hypertension, diabetes mellitus, myocardial infarction, stroke, history of smoking, and other ocular risk factors were recorded. Disease related variables including diagnosis and type of lesion, treated eye details, status of the lens, and presence of drusen were documented. The efficacy assessments included the best corrected visual acuity (BCVA) measured by a Snellen chart [converted to log MAR (Log of minimum angle of resolution) for analysis], decrease in central subfield thickness (CSFT, measured by spectral-domain optical coherence tomography [SD-OCT]), and intra-retinal fluid (IRF) and sub-retinal fluid (SRF) from baseline to weeks 1, 4, 8, 12, 24 and 48. Safety assessments were documented in terms of change in intraocular pressure and other adverse events (AEs).

Sample size and statistical analysis

In this real-world study, patients' data was collected retrospectively without any predetermined sample size. The study did not test any hypothesis and only the observations from patient's records were analyzed. The data collected from all the centers across India were compiled and statistical analysis was performed at Lambda Therapeutic Research Ltd., Ahmedabad, India. Demographic and baseline characteristics were summarized using descriptive statistics. Categorical variables were summarized with frequency and percentage. Continuous variables were summarized with count, mean, standard deviation, etc. Graphical presentation of data was done using bar chart as appropriate. Statistical analyses were performed using SAS® version 9.4 (SAS Institute Inc., USA).

Ethics statement

This retrospective study protocol carried less than minimal risk according to the Indian council of medical research 'Ethical guidelines for biomedical research on human participants'.[11] The study was conducted after due approval from the OM Institutional Ethics Committee, Ahmedabad, India. This was a retrospective study without patient identifiers; hence, the informed consent of patients was not taken. There was no confidentiality breach of the data during its analysis and interpretation.

RESULTS

Data of 1422 Indian patients and 1520 eyes, with retinal diseases including wet AMD, DME, RVO and mCNV, who were treated with biosimilar ranibizumab, was included for analysis in this study. Table 1 provides the demographic details of patients in this study.

The patients had a mean (SD) age of 60.61 (11.20) years. The most common age group of patients having retinal diseases was 61-70 years (36.6%) followed by 51-60 years (28.2%), 71-80 years (14.8%) and 41-50 years (12.4%). Most patients were males (62.31%) while females constituted 37.69% of the study population. Overall, 54.01% eyes were phakic, 44.37% eyes were pseudo-phakic and 1.62% eyes were aphakic. Right eye was treated in 50.91% of patients, left eye was treated in 42.19% of patients and both eyes were treated in 6.89% of patients. The most common ocular risk factor

identified was glaucoma (24.90%) followed by retinal pigment epithelial (RPE) abnormalities (22.4%), atherosclerotic retinal artery (9.3%), wet AMD in fellow eye (8.5%), high myopia of ≥-6D (7.6%) etc.

Table 1: Patient characteristics, (n=1422).

Parameters	Values
Age (years), mean (SD)	60.61 (11.20)
Age group (years), N (%)	
<40	74 (5.2)
41 to 50	177 (12.4)
51 to 60	400 (28.1)
61 to 70	520 (36.6)
71 to 80	211 (14.8)
> 80	40 (2.8)
Gender, N (%)	
Men	886 (62.31)
Women	536 (37.69)
Status of lens, N (%)	
Phakic	768 (54.01)
Pseudo phakic	631 (44.37)
Aphakic	23 (1.62)
Treated eye, N (%)	
Right	724 (50.91)
Left	600 (42.19)
Both	98 (6.89)
Drusen status, N (%)	
Present	250 (17.58)
Absent	1172 (82.42)
Comorbid conditions, N (%)	
Hypertension	1001 (70.39)
Diabetes mellitus	827 (58.16)
Myocardial infarction	98 (6.89)
< 3 months	3 (0.21)
3-6 months	4 (0.28)
6-12 months	18 (1.27)
>1 year	73 (5.13)
History of smoking, N (%)	
Yes	408 (28.69)
No	1014 (71.31)

Diagnosis and type of lesion

Out of 1422 patients, wet AMD was diagnosed in 392 (27.57%) patients, DME was diagnosed in 407 (30.7%) patients, RVO was diagnosed in 476 (33.47%) patients and mCNV was diagnosed in 74 (5.48%) patients (Table 2).

Treatment patterns

A total of 1219 (85.72%) patients were treatment naïve and remaining 203 (14.28%) patients were previously treated with other intravitreal anti-VEGF injections or intravitreal triamcinolone acetonide (IVTA) injection. Out of 1422 patients, majority (41.6%, n=592) patients received three biosimilar ranibizumab injections.

Table 2: Type of retinal disease, (n=1422).

Type of retinal disease	Patients, N (%)
Wet AMD	392 (27.57)
Classic	146 (10.27)
Minimally classic	21 (1.48)
Occult	112 (7.88)
Sub foveal	89 (6.26)
Juxta foveal	16 (1.13)
Extra foveal	8 (0.56)
DME	407 (28.62)
Diffuse DME	134 (9.42)
CSME	114 (8.37)
Mixed DME	96 (6.75)
Focal	63 (4.7)
RVO	476 (33.47)
BRVO	250 (17.58)
CRVO	149 (10.48)
HRVO	17 (1.20)
Ischemic	22 (1.55)
Non-ischemic	38 (2.67)
Myopic CNV	74 (5.20)
Extra foveal	2 (0.14)
Juxta foveal	14 (0.98)
Sub foveal	58 (4.08)
Other*	73 (5.13)

*Other category patients were: PCV (polypoidal choroidal vasculopathy), CNVM (choroidal neovascular membrane) secondary to parafoveal telangiectasia, CNVM with PFT (perifoveal telangiectasia), chronic CSCR (central serous chorioretinopathy), CSCR with CNVM, CSCR with CME (cystoid macular edema), idiopathic CNVM, idiopathic PCV with bleed with sub-retinal fluid (SRF) with exudation, large PED (pigment epithelial detachment) with exudation, neovascular glaucoma, previtreal hemorrhage, sub hyaloid hemorrhage, and vitreous hemorrhage. BRVO-branch retinal vein occlusion; CRVO-central retinal vein occlusion; CSME-clinically significant macular edema; HRVO-hemi retinal vein occlusion; RVO-retinal vein occlusion.

Efficacy assessments of biosimilar ranibizumab

BCVA

Mean BCVA (log MAR) at week 48 was 0.31±0.37 log MAR as compared to 0.85±0.43 log MAR at baseline for all indications indicating significant ($p<0.0001$) improvement in visual acuity after biosimilar ranibizumab administration (Figure 1). Similarly, significant ($p<0.0001$) improvements were reported in log MAR BCVA values for wet AMD, DME, RVO and mCNV indications after biosimilar ranibizumab administration (Figure 2).

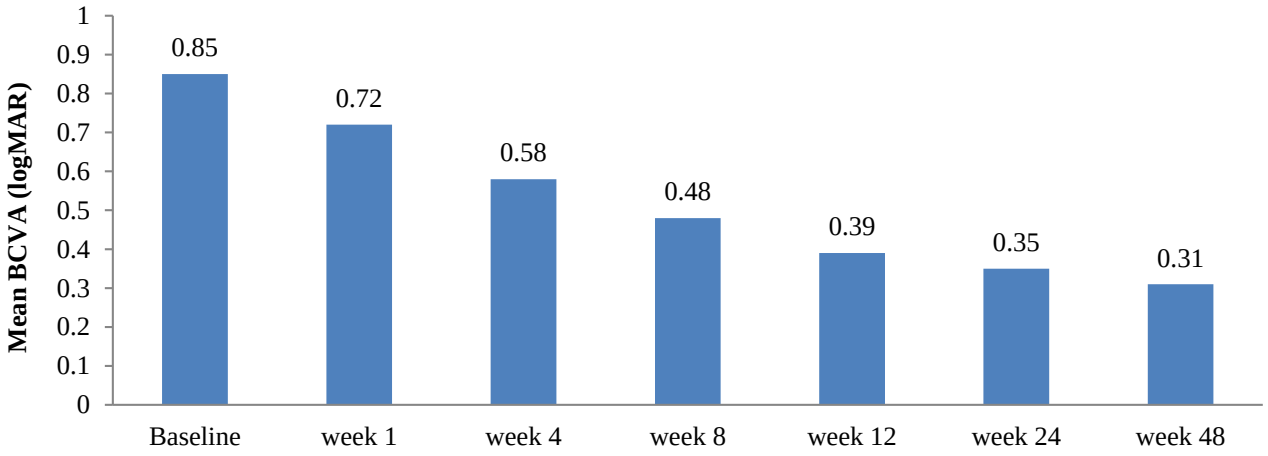

Figure 1: Mean BCVA (log MAR) at baseline and till week 48 after biosimilar ranibizumab administration.

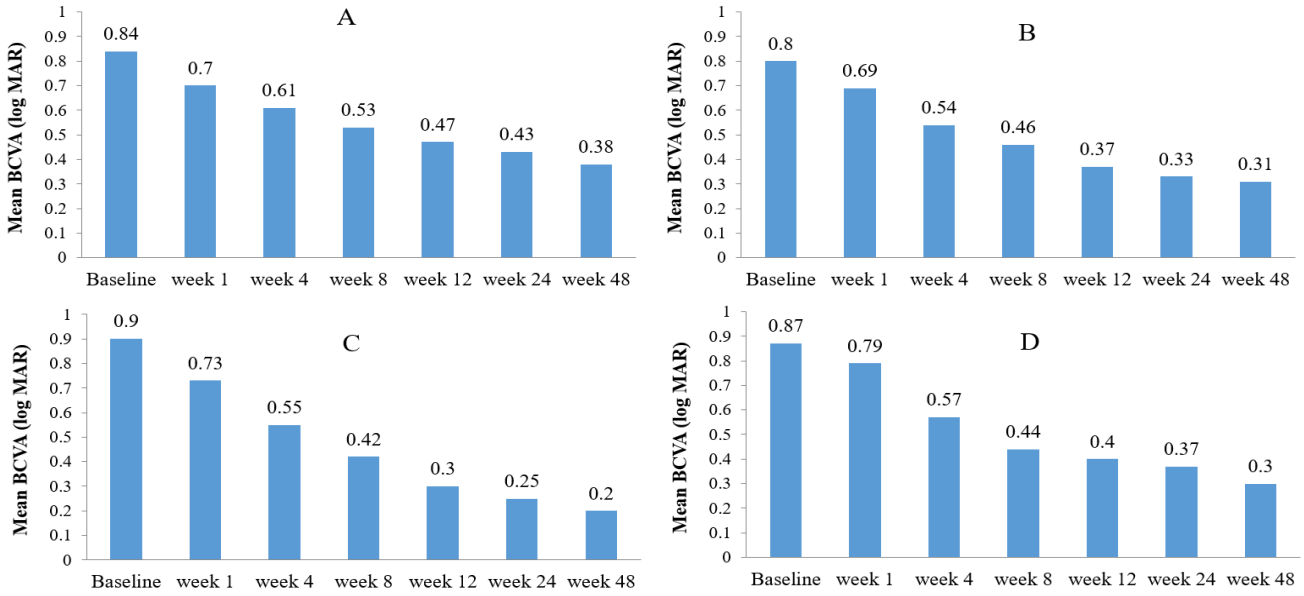

Figure 2 (A-D): Mean BCVA (log MAR) at baseline and till week 48 after biosimilar ranibizumab administration in patients with (A) wet AMD, (B) DME, (C) RVO, and (D) mCNV.

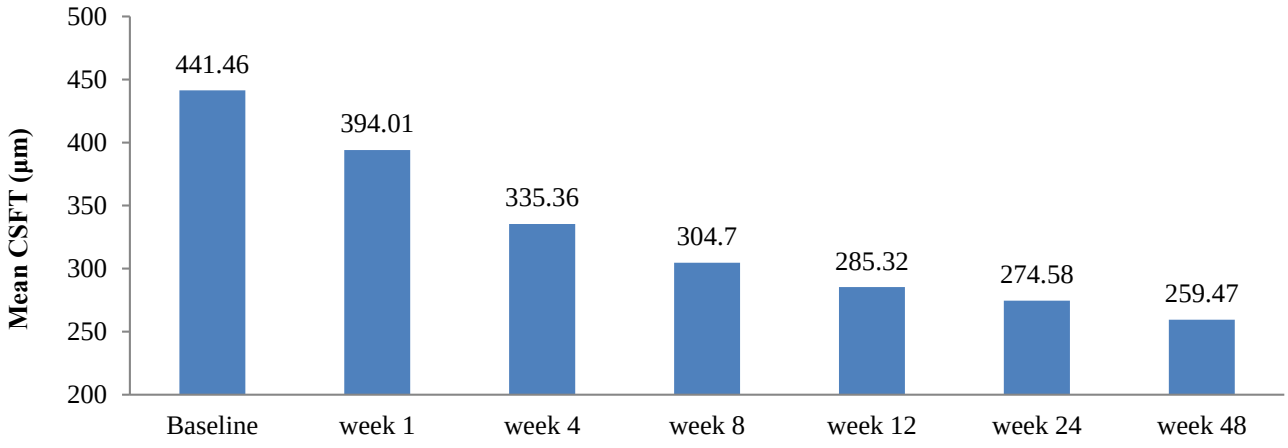

Figure 3: Mean CSFT (µm) at baseline and till week 48 after biosimilar ranibizumab administration.

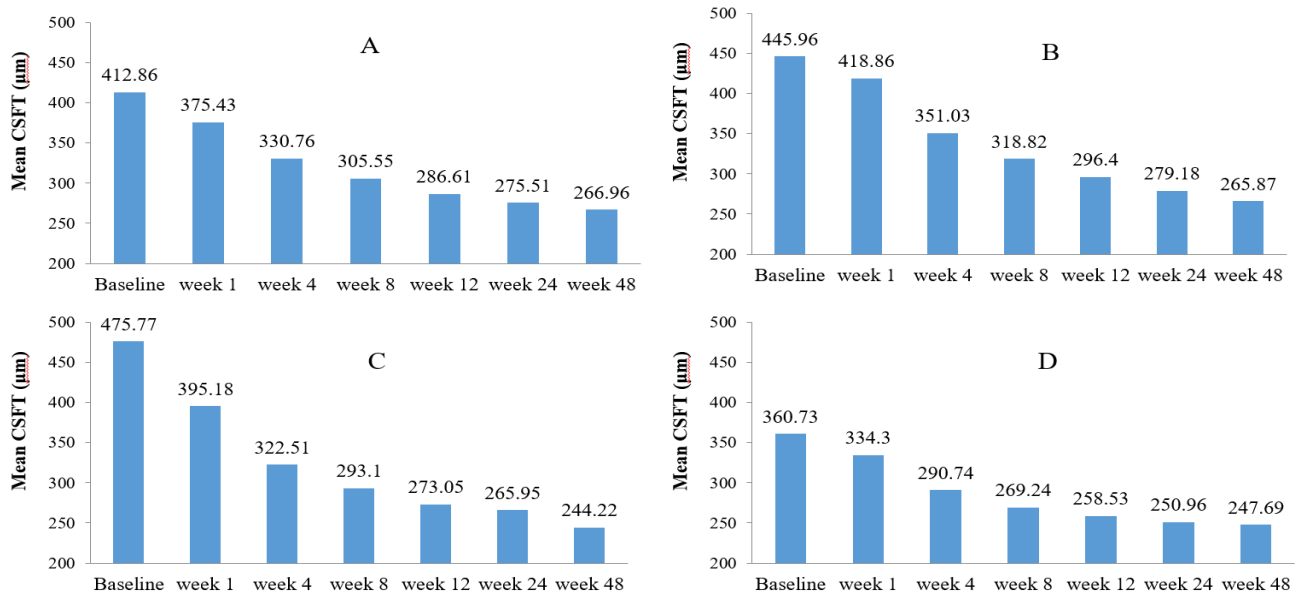

Figure 4 (A-D): Mean CSFT (µm) at baseline and till week 48 after biosimilar ranibizumab administration in patients with (A) wet AMD, (B) DME, (C) RVO, and (D) mCNV.

CSFT

The CSFT was reduced to 259.47±118.89 µm at week 48 as compared to 441.46±145.00 µm at baseline for all indications indicating significant ($p<0.0001$) improvement in the disease condition after biosimilar ranibizumab administration (Figure 3). Similarly, significant ($p<0.0001$) improvements were reported in CSFT for wet AMD, DME, RVO and mCNV indications after biosimilar ranibizumab administration (Figure 4).

IRF and SRF

Post biosimilar ranibizumab treatment, the percentage of patients with IRF and SRF significantly reduced from baseline to week 48 for all indications. The percentage of patients with IRF was significantly ($p<0.05$) reduced to 30.75% at week 48 as compared to 72.38% at baseline for wet AMD, 34.67% at week 48 as compared to 74.37% at baseline for DME, 28.16% at week 48 as compared to 64.29% at baseline for RVO and 21.15% at week 48 as compared to 61.67% at baseline for mCNV.

The percentage of patients with SRF was significantly ($p<0.05$) reduced to 27.83% at week 48 as compared to 65.35% at baseline for DME, 27.91% at week 48 as compared to 77.96% at baseline for wet AMD, 27.83% at week 48 as compared to 65.35% at baseline for DME, 24.82% at week 48 as compared to 57.52% at baseline for RVO and 24.07% at week 48 as compared to 63.49% at baseline for mCNV.

Safety assessments of biosimilar ranibizumab

There was no clinically significant change in IOP (mm Hg) at weeks 1, 4, 8, 12, 24 and 48 as compared to baseline. Most of the patients had no AEs (98.37%). A total of 22 AEs were reported in this study and conjunctival hyperemia was the most common (15 AEs) among them. All the AEs were mild (n=20) or moderate (n=02) in nature and resolved without any sequelae.

DISCUSSION

The pathophysiology of retinal diseases such as wet AMD, DME, RVO and mCNV involve VEGF pathways and the anti-VEGF agents including ranibizumab, aflibercept, brolucizumab and bevacizumab (off-label), have changed the management paradigm of these retinal diseases. These anti-VEGF agents are known to improve vision along with the prevention of vision loss leading to significantly improved prognosis and outcomes, and eventually improved quality of life.[12-16] The current retrospective observational study evaluated the potential risk factors associated with retinal diseases in the Indian population. This study also provides the efficacy and safety data of Indian patients with retinal diseases who were treated with biosimilar ranibizumab. The results of this study have proven that the treatment with biosimilar ranibizumab demonstrated significant improvements in the visual acuity, central subfield thickness, IRF and SRF from baseline to week 48 with a well-tolerated safety profile in Indian patients with retinal diseases.

Wet AMD is a leading cause of vision loss, particularly in the elderly population.[17-19] In India, wet AMD is a cause of public health concern due to a rapidly increasing ageing population.[20] RVO leads to unilateral and painless vision loss.[21,22] DME is a major cause of vision loss in diabetic individuals.[23] mCNV is rare but may result in an irreversible vision loss.[24,25] In the present study of 1422 patients and 1520 eyes, the prevalence of retinal diseases

was high in the age group of 61-70 years and in males. Ageing, diabetes, hypertension, smoking, ≥-6D high myopia, glaucoma, retinal pigment epithelial (RPE) abnormalities, atherosclerotic retinal artery etc. are some common risk factors for several retinal diseases.[26] In our study, glaucoma was the most common ocular risk factor for retinal diseases followed by RPE abnormalities, atherosclerotic retinal artery, wet AMD in fellow eye, high myopia of ≥-6D etc. The common associated comorbidities were hypertension (70.3%), diabetes mellitus (58.16%) and myocardial infarction (6.89%) in this present study. Presence of drusen and its measurement may serve to identify risk for progression of early AMD to late AMD.[27] In this present study, drusen was present in 17.58% of the patients.

Ranibizumab, a humanized monoclonal antibody fragment improves the visual acuity by binding to VEGF-A isoforms, and hence, is considered treatment of choice for retinal diseases.[28-31] A biosimilar ranibizumab was developed by Intas Pharmaceuticals Limited, Ahmedabad, India to overcome the unaffordability of the innovator ranibizumab.[32] The efficacy and safety of biosimilar ranibizumab in retinal diseases such as wet AMD, DME, RVO and mCNV have been reported in several prospective and retrospective studies in Indian patients.[33] The real-world efficacy and safety of biosimilar ranibizumab in retinal diseases was reported in the RE-ENACT (n=561) and RE-ENACT 2 (n=341) studies.[33]

In this current study, the mean BCVA and CSFT showed significant improvements ($p<0.0001$) in the visual acuity and disease condition. Also, the percentage of patients with IRF and SRF significantly reduced from baseline to week 48 for all indications after biosimilar ranibizumab treatment. This observational study results are in accordance with the RE-ENACT 2 study in patients with wet AMD, DME, RVO and mCNV with a follow-up duration of 48 weeks. Treatment with biosimilar ranibizumab resulted in significant improvements ($p<0.001$) from baseline to week 48 in the BCVA (0.89±0.6 vs. 0.43±0.3 log MAR) values and CSFT (467.09±159.6 vs. 296.56±49.7 µm).[34] The current study provides the results from a comparatively larger pool of patients (n=1422) and eyes (n=1520) with a similar long-term follow-up data (48 weeks). The CESAR study in patients with DME, RVO and mCNV reported significant improvement in visual acuity and central foveal thickness (CFT) as early as 1 month after initiating biosimilar ranibizumab treatment.[35] The present study results are in accordance with the CESAR study findings.

In the present study, 85.72% patients were treatment naïve while 14.28% patients were previously treated with another intravitreal anti-VEGF injection or intravitreal triamcinolone acetonide (IVTA) injection. In comparison to parent biologic drugs, biosimilar agents lead to 25-50% reduction in the treatment cost.[33] It has been reported that Intas' Razumab™, biosimilar ranibizumab, (US $125) is a cost-effective alternative to the innovator ranibizumab (US $320), aflibercept (US $760) and brolucizumab (US $350).[36]

No clinically significant change in IOP (mm Hg) after biosimilar ranibizumab treatment was noted during the study duration. Most of the patients had no AEs (98.37%). A total of only 22 AEs (mild [n=20] or moderate [n=02]) were noted and all the AEs were resolved without any sequelae. The results are in accordance with the RE-ENACT and RE-ENACT 2 studies, which demonstrated that biosimilar ranibizumab was effective and well-tolerated, with no new safety concerns, in retinal diseases in the real-world Indian settings.[33]

The study limitation included a retrospective nature of the study, and data entry at multiple sites potentially leading to inconsistency in the data.

CONCLUSION

In the current retrospective real-world REAR RD-2 study, glaucoma was the most common ocular risk factor for retinal diseases in Indian patients followed by RPE abnormalities, atherosclerotic retinal artery, wet AMD in fellow eye, high myopia of ≥-6D etc. Further, this study strengthens the use of Razumab™, biosimilar ranibizumab, in real-world clinical settings as a cost-effective anti-VEGF agent that showed clinically significant improvements in visual acuity and disease conditions for a longer follow-up duration of 48 weeks in patients with retinal diseases including wet AMD, DME, RVO and mCNV without any new safety issues. Razumab™ (biosimilar ranibizumab) with its cost effectiveness, without compromising efficacy and safety, can be considered as a valuable alternative to the other approved anti-VEGF agents in patients with retinal diseases in the developing nations, with limited resources, like India.

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Conflict of interest: Dr. Shashikant Sharma, Dr. Alok Chaturvedi and Dr. Nilanj Dave are employees of Intas Pharmaceuticals Limited, Ahmedabad, Gujarat, India. Ms. Ankita Shah is an employee of Lambda Therapeutic Research Ltd., Ahmedabad, Gujarat, India
Ethical approval: The study was approved by the Institutional Ethics Committee

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