



Original Research Article

A comparative study between ranibizumab and its first biosimilar razumab in terms of efficacy and safety in DME, RVO and wet AMD associated with CNVM

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ABSTRACT

Purpose: To compare safety and efficacy of intravitreal therapy between anti vascular endothelial growth factor (Anti-VEGF) Ranibizumab and biosimilar Razumab in diabetic macular oedema (DME), wet age related macular degeneration (AMD) with choroidal neovascular membrane (CNVM) and retinal vein occlusion (RVO).

Methods: Prospective comparative study involved 60 eyes of 56 adults, randomized into 2 groups from September 2016 to November 2017. Group 1 (n=30) received Ranibizumab (0.5mg in 0.05ml) and group 2(n=30) Razumab (0.5mg in 0.05ml). Initial loading dose of one injection given to all subjects and a pro re nata schedule followed thereafter. Patients received maximum of 3 injections and were followed up to 12 weeks. Best corrected visual acuity (BCVA) and central foveal thickness (CFT) were considered for the primary outcome and adverse drug reactions (ADR) was considered in the secondary outcome. A p value of less than 0.05 was considered statistically significant.

Results: The 12-week mean BCVA in group 1 was 0.39 (+0.24); and in group 2 was 0.53 (+0.37), which had improved significantly from baseline (group 1 p= 0.007, group 2 p <0.001). Inter group comparison was statistically insignificant (p=0.249). The 12 weeks mean CFT in group 1 was 308 (+107.26) ; and group 2 was 307.60 (+ 87.15), which had improved significantly from baseline in both groups (p <0.001). Inter group difference was statistically insignificant (p=0.544). One patient in group 2 experienced an ADR (p=0.305).

Conclusion: In this study both Ranibizumab and Razumab were safe and efficacious.

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1. Introduction

Anti VEGF such as Ranibizumab has been a major breakthrough in the treatment of various retinal disorders such as DME, CNVM & macular oedema secondary to RVO, where VEGF plays a prime role in the disease pathogenesis. DME is one of the leading causes of visual impairment in the working-age population in many countries. The prevalence of DME increases from 0% to 3% in individuals with recent diagnoses of diabetes and about 28% to 29% in those with diabetes for more than 20

years.¹⁻⁴ RVO is the second most common cause of retinal vascular disease after diabetic retinopathy, the prevalence of RVO is approximately at 16 million.^{5,6} CNVM is usually seen in the elderly age group and macular CNVM is one of the leading causes of blindness world over. The burden of these diseases in the Indian subcontinent is high, factoring its high morbidity and contributing to major causes of retinal blindness.⁷⁻⁹ With the advent of anti VEGF drugs, an efficacious and safe treatment of these diseases is possible. Ranibizumab was approved in 2006, by the US Food and Drug Administration(FDA) under the brand name Lucentis® (Genentech/Novartis), developed specifically for intraocular use.^{1,10} However the higher cost prices of the

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drug lead to the development of a market for biosimilars known by the brand name Razumab(Intas Pharmaceuticals). It is the first ophthalmic biosimilar developed in India which has been approved by the Drug Controller General of India (DCGI) for the use in DME, RVO, myopic CNVM and wet AMD.¹¹ Biosimilars are defined as biologic products that are highly like reference products, notwithstanding minor differences in clinically inactive components, with no clinically meaningful differences between the biologic product and the reference product in terms of safety profile, purity, and potency.¹²

Several studies are available with regards to the safety and efficacy of Ranibizumab.^{13,14} The number of studies on Razumab is fewer, let alone a comparative study among the two drug groups.^{11,14,15} Thus in this study we compare the safety and efficacy between the 2 drugs.

2. Materials and Methods

A prospective interventional comparative study conducted at an urban tertiary health care centre in south India. The study followed the tenets of the declaration of Helsinki and was approved by our ethics committee. The choice of preference of drug was made by the patients themselves as considerable cost difference was involved. Subjects were chosen in group 1 Ranibizumab initially and matched with group 2 Razumab based on disease etiology to avoid confounding. Though we included subgroup analysis with 10 patients in each subgroup of the respective drugs, due to small sample size of the subgroups it does not account for statistically significant number for this study.

Patients diagnosed with DME, RVO with macular oedema or wet AMD with CNVM, received a minimum of one injection of either Ranibizumab or Razumab. The study was conducted from September 2016 to November 2017. The maximum number of injections per patient considered in this study was limited to three. The need for treatment with anti-VEGF and further number of injections was made by the treating surgeon based on clinical examination and aided by OCT imaging. Standard postoperative care was given to all cases.

Subjects were treatment naive. Patients excluded were those with other coexistent retinal pathologies, proliferative diabetic retinopathy, media opacities impairing vision such as significant cataract, corneal opacities and those who were unable to comply with the study or follow up.

The study end points included BCVA (converted from Snellens to LOGMAR at myvisiontest.com), CFT, optical coherence tomography (OCT) Line scan and thickness scan at baseline, 4 and 12 weeks. OCT scans evaluated decrease in sub retinal fluid (srf) and intra retinal fluid(irf). A grading system was designed by us specifically for the study in terms of improvement in visual acuity and OCT (Table 1 and 2 respectively). The evaluation and scoring were done by a retina consultant who was double blinded in order

to minimise observer bias and played a crucial role in determining the study outcome.

Ocular adverse reactions such as ocular inflammation, endophthalmitis, iatrogenic cataract, retinal tears, retinal detachment, vitreous haemorrhage, persistent raised intra ocular pressure if any was documented.¹⁰

2.1. Statistical analysis

Descriptive studies were used to summarise the data and chi square test was used as test of significance for qualitative data. Independent t test or Mann Whitney U test for unpaired variables. Paired t test or Wilcoxon signed rank test was used as test of significance for paired individuals. p value of <0.05 was considered as statistically significant.^{14,16}

3. Results

A total of 60 eyes of 56 patients were analysed, that included 31 females and 29 males. In group 1 majority were males 53.3%, group 2 majority were females 56.7%. Mean age of subjects in group 1 was 66.9 and 64 in group 2. In both Ranibizumab and biosimilar group, 33.3% were diagnosed to have RVO, wet AMD associated CNVM and DME respectively (n = 10 in each subgroup).

A significant improvement in BCVA was observed from baseline to 12 weeks post injection in both groups (p values: group 1=0.007, group 2<0.001). Mean values with standard deviation for group 1 at pre injection was 0.56 (+-0.39) and group 2 was 0.78 (+-0.47) and at 12 weeks post injection 0.39 (+-0.24) and 0.53 (+-0.37) respectively. Whereas mean BCVA at baseline and 12 weeks post injection between groups 1 and 2 was statistically insignificant (baseline p=0.052, post injection p=0.249).

A significant improvement in CFT was observed from baseline to 12 weeks post injection in both groups (p values: group 1 and 2 <0.001). Mean values with standard deviation pre injection in group 1 was 479.90 (+- 211.20) and group 2 was 467.93 (+- 138.49) and at 12 weeks post injection was 308(+107.26) and 307.60(+ 87.15) respectively. Whereas mean BCVA at baseline and 12 weeks post injection between groups 1 and 2 was statistically insignificant (baseline p= 0.631, post injection p=0.544). The difference in OCT grading between two groups was comparable and statistically insignificant (p = 0.182).

A variability was noted in the number of injections received by patients, not all cases received a total of three injections because a set of patients improved with a lesser dose, thus there was no further indication to continue intravitreal anti-VEGF. These cases were closely monitored on follow up. The number of injections caused no bias in analysis of the results(p=0.670).

There was no ocular complications in group 1, in group 2 one subject with wet AMD associated CNVM developed severe ocular inflammation on postoperative day1 and was

started on topical steroid 1% prednisolone acetate with which the inflammation was well controlled and eventually subsided. There was no visual deterioration or worsening of disease condition and on follow up the patient showed an improvement in the OCT grading from fair to good and also a one line improvement in the logmar scale in terms of visual acuity. The complication was statistically insignificant ($p=0.305$).

Table 1: Grading of visual acuity in logmar units

Logmar line improvement	Grade
= > 4	Excellent
>= 2 TO < 4	Good
No improvement to 1 line improvement	Fair
Decrease in logmar line	Poor

4. Discussion

Ranibizumab is a humanized monoclonal antibody fragment (Fab), it acts by binding to VEGF-A with high affinity and inhibits multiple isoforms of VEGF-A and also has a well proven efficacy and safety.^{10,16,17} A number of studies are available for Ranibizumab, such as the ANCHOR, MARINA, PIER, PRONTO, VISION, LEVEL, CATT, CLEAR-IT for AMD, the CRUISE and BRAVO studies for macular oedema after RVO, the RESOLVE, RESTORE, READ-2, and DA VINCI studies for DME.^{18–28} Though efficacious and safe the high cost of the drug and has lead to the use of biosimilars.

The RE-ENACT 2 multicentric retrospective study investigated by doctors of Intas pharmaceuticals showed significant improvement in BCVA, CFT, Irf and srf, in patients with wet AMD, DME, RVO and myopic CNVM, the follow up duration was 48 weeks. A study published by Sameera et al.,¹⁴ was a prospective analysis on 123 eyes of 95 patients with DME, neovascular AMD and macular oedema secondary to RVO who were treated with Razumab. Primary and secondary outcome measures were safety parameters that included signs of clinical and ERG toxicity and changes in BCVA and central macular thickness (CMT). The study concluded that the biosimilar was tolerated over a month with improvements in BCVA and CMT without detectable ocular or systemic toxicity.

Our study was undertaken as there were no comparative studies between Ranibizumab and its biosimilar for intravitreal use. In our study both groups at 12 weeks post injection showed improvement in visual acuity (p values: group 1= 0.007, group 2<0.001). In the grading system designed by us for analysis of improvement in visual acuity, patients in both the groups did equally well, with no statistical significant difference between them ($p=0.584$ at 12 weeks post injection). CFT at 12 weeks post injection in both groups demonstrated a decrease in CFT (p values: group 1 and 2 <0.001). Analysing the OCT grading

system designed by us for the study there was no significant difference in OCT results between the two groups ($p = 0.182$). Therefore, in terms of improvement in vision and reduction in macular oedema our study results corroborated with the above mentioned studies.

A comparative analysis of logmar BCVA, CFT, OCT grading between the two groups was not statistically significant, thus concluding the two drugs were comparable in terms of these variables to various studies as mentioned before.

In our study we encountered a complication of ocular inflammation in the biosimilar group in the immediate post-operative period that was managed effectively, and the drug batch withdrawn. The reason attributing to the ADR was found to be due to an increase in the levels of bacterial endotoxin.²⁹ The major difference between generic drugs and its biosimilar is that, generic drugs are manufactured based on matching the chemical formula and synthesis, whereas the manufacturing of biosimilars such as Razumab will not have access to manufacturing process of innovator products, as this is a proprietary knowledge.^{29–33} Razumab manufacturing involves living cells (*Escherichia coli* expression system) in the process and even a slight change from the originator molecules for example protein folding can readily modify its safety and efficacy. Thus, it will be difficult to accurately duplicate any protein product.^{34–36} Extrinsic endotoxins can be attributed to improper sterilization and storage, whereas intrinsic endotoxins originate during inherent drug manufacturing process.²⁹

A presentation from the market research 2017 in the vireo-retinal society of India website³⁷ demonstrated there are significant variations in the cost of treatment between Ranibizumab and its biosimilar. Quoting from a newspaper article, published in December 2017, the data from the 60th round of the National Sample Survey, conducted in 2004, had shown that 70% of out-of-pocket expenditure is on medicines. The Health in India report showed that in rural India, 25% of patients relied on “borrowings” for hospitalisation expenses. The dosing of the Anti-VEGF in our study reflects the real life day to day patient scenario. Thus in Indian subcontinent where the burden of blindness is significant due to diabetic retinopathy, retinal vein occlusion and choroidal neovascular membrane and given that anti-VEGF’s are the first line of treatment, Razumab can be considered as an alternative to Ranibizumab. Adhering to safety standards and reporting of each case of an ADR is of prime importance.

Limitation of study was the short-term duration of 3 months; thus, further outcomes in terms of antigenicity, tachyphylaxis and tolerance of the biosimilar is unknown.³⁸

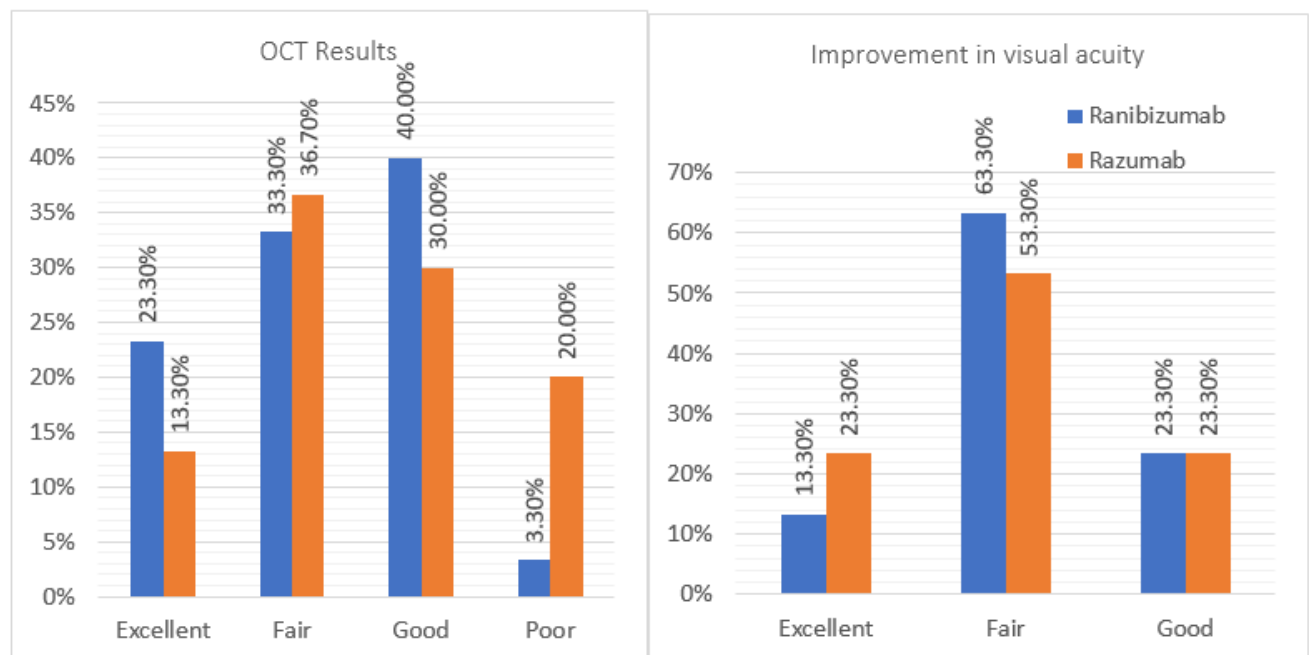
Table 2: Grading of OCT

Grade	RVO	Wet AMD associated CNVM	DME
Excellent	Resolved fluid. No structural abnormality	Resolved fluid. Regressed/ Scarred CNVM	Resolved Fluid. No Structural Abnormality
Good	Resolved fluid. Mild structural abnormality	Minimal Residual Fluid, with Structural Abnormality	Resolved Fluid with Mild Structural Abnormality
Fair	Persistent Fluid but with Partial Resolution as Compared to Previous Scans	Persistent fluid which has decreased as compared to previous scans	Persistent fluid but with partial resolution as compared to previous scans
Poor	Non-resolution/increasing fluid	Non-resolution/increasing fluid	Non-resolution/increasing fluid

Table 3: Assessment of mean BCVA and CFT between groups 1 and 2 at baseline and 12 week follow up

	Baseline	12 weeks
Mean BCVA group 1	0.56	0.39
Mean BCVA group 2	0.78	0.53
Difference between groups(p)	0.052	0.249
mean CFT group 1	479.90	308
mean CFT group 2	467.93	307.60
Difference between groups(p)	0.631	0.544

BCVA: in logmar units, CFT in microns

**Fig. 1:** Bar diagrams representing the grading scale designed by us for OCT and improvement in visual acuity at 12 weeks follow up for the 2 drug groups

5. Conclusion

In our study the biosimilar of Ranibizumab was equally effective and efficacious as the parent drug. Use of biosimilars need vigorous pharmacovigilance and more such trials should be undertaken to establish their role in retinal ocular diseases.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

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