

## ORIGINAL ARTICLE

## SHORT-TERM EFFICACY OF INTRAVITREAL PATIZRA® (RANIBIZUMAB) IN TREATMENT NAIVE PATIENTS- REAL WORLD EVIDENCE IN PAKISTAN

Hajra Arshad Malik<sup>1</sup>, Rayyan Sabih<sup>1</sup>, Hina Khan<sup>1</sup>, Muhammad Umair<sup>2</sup>, Muhammad Asif<sup>3</sup>,  
Aamir Asrar<sup>1</sup>, Maha Asrar<sup>1</sup>

<sup>1</sup>Amanat Eye Hospital Islamabad, <sup>2</sup>Combined Military Hospital Rawalpindi, <sup>3</sup>Government College University Faisalabad-Pakistan

**Background:** Macular oedema is a final common pathway of a multitude of both ocular and systemic insults. This study was conducted to evaluate the short-term efficacy and safety of intraocular Ranibizumab in patients with macular oedema in a 'real-world' setting in Pakistan.

**Methods:** A prospective multicenter study conducted at Amanat Eye Hospitals in Islamabad and Rawalpindi from 1<sup>st</sup> August 2018 to 1<sup>st</sup> November 2019. Forty-four eyes of 34 patients with macular oedema were treated with monthly intravitreal Ranibizumab (Patizra®) injections for three consecutive months. Best-corrected visual acuity (BCVA), and optical coherence tomography (OCT) parameters including central retinal thickness (CRT) and macular volume were assessed prior to the injections and then 4 weeks post the final injection and compared. **Results:** BCVA improved from logMAR 0.61±0.40 at baseline to 0.27±0.35 four weeks after the third intravitreal injection. CRT decreased from 428.54±187.06 µm at baseline to 364.50±170.49 µm. Macular volume showed a non-significant decrease from 9.97±3.19 mm<sup>3</sup> at baseline to 9.22±2.68 mm<sup>3</sup> four weeks after the third intravitreal injection. No systemic or ocular complications were observed during the course of the study. **Conclusion:** Treatment with intravitreal Patizra® injections was found safe and resulted in clinically and statistically significant improvement in visual acuity and the SD-OCT parameter of central retinal thickness in patients with macular oedema secondary to various retinal pathologies. There was no significant decrease in the macular volume.

**Keywords:** Ranibizumab; Macular Oedema; Diabetic Retinopathy; Macular Degeneration; Retinal Vein Occlusion

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### INTRODUCTION

Macular oedema can be a potential outcome of a wide array of pathological conditions<sup>1</sup> and represents the final common pathway of a multitude of both intraocular and systemic insults<sup>2</sup>. Common diseases associated with macular oedema include diabetic retinopathy (DR), retinal vein occlusion (RVO), choroidal neovascularization (CNV), and uveitis.<sup>3</sup>

Vascular endothelial growth factor (VEGF) production is induced by hypoxia<sup>4</sup> and mediates vascular permeability, ultimately contributing to macular edema<sup>5</sup>. In view of this, the introduction of anti-vascular endothelial growth factor (anti-VEGF) injections such as Bevacizumab, Ranibizumab and Aflibercept has revolutionized the treatment of macular oedema and is one of the most promising approaches to the management and prevention of its possible detrimental effects.<sup>6,7</sup> Recently, Ranibizumab has been introduced for sale in Pakistan under the label of Patizra® (Novartis) as opposed to the previously available Lucentis® (Novartis). According to the manufacturer, the compound

remains unchanged and the main purpose of the change in name is to supply the compound at a subsidized rate to Pakistani consumers. A large number of studies has been conducted globally pertaining to the efficacy of the Ranibizumab molecule (Lucentis®, Novartis Pharma AG, Basel, Switzerland; Genentech Inc., San Francisco, CA, USA).<sup>8-12</sup> No study, however, has been conducted in Pakistan to date to ascertain the effectiveness of Patizra® compared to that of Lucentis®.

Patizra® is being marketed in Pakistan for the past two years, and it is being used on the same guidelines (indications, dosing and scheduling) as Lucentis®. In our study, we prospectively evaluated the efficacy of Patizra® in patients with various retinal pathologies that warranted anti-VEGF therapy.

### MATERIAL AND METHODS

This was a prospective multicenter interventional study. The study was conducted at two branches of Amanat Eye Hospital in Rawalpindi and Islamabad

between 1<sup>st</sup> August 2018 and 1<sup>st</sup> November 2019. All cases in this study were Pakistani individuals between the ages of 34–71, recruited from Amanat Eye Hospital branches in Islamabad and Rawalpindi. We examined 44 'treatment naive' eyes of 34 patients with various symptomatic retinal pathologies including DR, RVO, and CNV which provided an indication for treatment with anti-VEGF injections.

Our study included patients with retinal pathologies associated with macular oedema observed on optical coherence tomography (OCT) or leakage on fluorescein angiography. We excluded: 1) Patients with NVE (Neovascularization Elsewhere) and PDR (Proliferative Diabetic Retinopathy) with no macular oedema; 2) patients who switched to alternative anti-VEGF compounds prior to the completion of three consecutive monthly injections of Patizra<sup>®</sup> or switched to treatment options other than VEGF inhibitors such as *Ozurdex*<sup>®</sup> (dexamethasone intravitreal implant, Allergan, Inc., Irvine, CA) and 3) those who received any other treatment, including thermal laser photocoagulation, submacular surgery, any other anti-VEGF intravitreal drugs, and photodynamic therapy prior to receiving the Patizra<sup>®</sup> treatment.

Ethical approval was obtained from the medical ethics board at Amanat Eye Hospital. This study adhered to the tenets of the Declaration of Helsinki and informed written consent was obtained before the investigation began.

Patients were recruited following initial assessment and informed written consent was obtained. A detailed questionnaire on the patients' demographic data including age, gender, the presence or absence of hypertension and diabetic mellitus, and a history of nephropathy, ischemic heart disease, hypercholesterolemia, as well as additional ocular treatment such as PRP, ocular surgery, or previous anti-VEGF injections was obtained. All patients received detailed ophthalmic examinations, including best-corrected visual acuity (BCVA) measurements with Snellen chart (BCVA measurements were converted to logarithm of the minimum angle of resolution [logMAR]) and slit lamp bio-microscopy. The patients then underwent colour fundus photography, fluorescein angiography (FA), and OCT prior to the first anti-VEGF injection. Central retinal thickness (CRT) and macular volume values were recorded from the SD-OCT. The diagnosis was established based on this assessment. All patients were administered three consecutive intravitreal Patizra<sup>®</sup> injections at 04 weekly intervals, and were then scheduled for a follow up visit four weeks post the third intravitreal injection. At this final visit, their BCVA was reassessed, followed by CRT and macular volume values recorded from the SD-OCT.

If patients required more anti-VEGF injections post their third Patizra<sup>®</sup> injection, the additional injections were excluded from the data to maintain uniformity of treatment among the sample.

The data was analyzed by using SPSS version 23. The descriptive variables were presented as frequencies, percentages, mean and standard deviation. The BCVA, CRT and macular volume were compared before and after intravitreal Patizra<sup>®</sup> injection by using Paired t-test. At 95% confidence interval, the *p*-value <0.05 was considered as showing statistically significant results.

## RESULTS

In total, 44 eyes of 34 patients were analyzed. The patients had a mean age±SD of 58.8±9.4 years and were predominantly 34 (77.3%) males. Thirty-two (72.7%) patients had concomitant co-morbidities, including 28 (63.6%) patients with hypertension, 14 (31.8%) with hypercholesterolemia, 6 (13.6%) suffering from nephropathy and 16 (36.4%) from ischemic heart disease. Sixteen (36.4%) patients also had glaucoma accompanying their retinal pathology. Thirty-eight (86.4%) patients had undergone alternative intervention pertaining to their ocular disease, including 34 (77.3%) patients who underwent PRP, 2 (4.5%) who underwent grid macular laser, and 28 (63.6%) cataract surgery.

Of the 44 treated eyes, 36 exhibited diabetic retinopathies (DR) with diabetic macular oedema (DME), 4 had RVO, and 4 showed evidences of CNV. Mean BCVA (logMAR) at baseline was 0.6. In addition, the mean CRT at baseline was 428.5 µm and the mean macular volume at baseline was 9.9 mm<sup>3</sup>.

A Paired t-test was conducted to compare BCVA before and after intravitreal Patizra<sup>®</sup> injection. The mean BCVA assessed 4 weeks after the third intravitreal Patizra<sup>®</sup> injection was 0.27. A statistically significant vision gain was observed from baseline as 0.34 (*p*<0.05). Vision gain from baseline is presented in Table-1. The BCVA improved in 30 (68.2%) patients, stabilized in 6 (13.6%) patients, and deteriorated in 8 (18.2%) patients.

A Paired t-test was conducted to compare CRT before and after intravitreal Patizra<sup>®</sup> injection. The mean CRT value 4 weeks after the third intravitreal Patizra<sup>®</sup> injection was 364.5µm. As shown in Table-2, the mean CRT decreased significantly (*p*<0.05) compared with the baseline 428.5µm.

A Paired t-test was conducted to compare macular volume before and after intravitreal Patizra<sup>®</sup> injection. The mean macular volume 4 weeks after the third intravitreal Patizra<sup>®</sup> injection was 9.22 mm<sup>3</sup>,

and exhibited a non-significant decrease in trend ( $p>0.05$ ), as shown in Table-3.

One hundred and sixty-eight injections were administered to the patients in total. Thirty eyes (68.2%) did not require additional injections after three consecutive monthly injections of Patizra<sup>®</sup>. Fourteen eyes (31.8%) required additional injections. Among them, 2 eyes required 5 extra injections, 6 eyes needed 3 more injections, 2 eyes required an

additional 2 injections, and the remaining 4 eyes needed one extra injection of Patizra<sup>®</sup>. No patient was observed to develop ocular complications, including endophthalmitis, rhegmatogenous retinal detachment, intraocular pressure elevation, cataracts, RPE tears or ocular haemorrhage. In addition, no incidences of systemic side effects including cerebrovascular accident (CVA), myocardial infarction or allergic reactions were noted.

**Table-1: Paired t-test to compare BCVA before and after intravitreal Patizra<sup>®</sup> injection**

BCVA	Mean±SD	t (df)	p-value
Before intravitreal Patizra <sup>®</sup> injection	0.61±0.40	5.0	<0.001
After third intravitreal Patizra <sup>®</sup> injection	0.27±0.35	(43)	

**Table-2: Paired t-test to compare central retinal thickness before and after intravitreal Patizra<sup>®</sup> injection**

Central Retinal Thickness	Mean±SD	t (df)	p-value
Before intravitreal Patizra <sup>®</sup> injection	428.54±187.06	2.29	0.027
After third intravitreal Patizra <sup>®</sup> injection	364.50±170.49	(43)	

**Table-3: Paired t-test to compare macular volume before and after intravitreal Patizra<sup>®</sup> injection**

Macular Volume	Mean±SD	t (df)	p-value
Before intravitreal Patizra <sup>®</sup> injection	9.97±3.19	1.93	0.06
After third intravitreal Patizra <sup>®</sup> injection	9.22±2.68	(43)	

## DISCUSSION

The results of this prospective study establish that treatment with intravitreal Patizra<sup>®</sup> injections provided clinically and statistically significant improvement in SD-OCT parameters and visual acuity in patients with macular oedema secondary to various retinal pathologies in a ‘real-world’ clinical setting in Pakistan.

In our analysis, the mean average change in BCVA post intravitreal Patizra<sup>®</sup> injections was 0.34 (significant), 64.54 μm (significant) in the CRT and 0.75mm<sup>3</sup> (non-significant) in the macular volume. These findings are comparable with the results of various studies that have been conducted on Asian populations with regards to the effectiveness of Ranibizumab.

Visual and anatomic improvements with Ranibizumab treatment were observed in a non-interventional, retrospective cohort study of East-Asian patients with myopic choroidal neovascularization (mCNV) previously treated with Ranibizumab during the RADIANCE trial.<sup>13</sup> Mean visual gain from baseline BCVA (56.5±12.1 letters) (20/80) at 12 months was significant (+14.3±11.4 letters, n=40,  $p<0.0001$ )<sup>13</sup>, and similar to our findings. Consistent with our observation, another study conducted on South Asian patients with vision loss due to diabetic macular oedema to ascertain the effectiveness of Ranibizumab found that the mean baseline VA for the treatment-naïve eyes was 59.0±10.5 letters, which increased to 64.2±10.4 letters at 12 months. The mean baseline CRT of this

group was 519±131μm, which reduced to 331±107 μm at 12 months<sup>14</sup>. This study worked on average worse macular oedema and saw a higher range of improvement than our study. We believe this may be due to inclusion of multiple pathologies and more variation in the severity of oedema in our study. An important thing to note was that although some patients did not have a significant improvement in their BCVA, they did exhibit a substantial decrease in the CRT and macular volume. This lack of improvement in visual acuity could be owing to other concomitant ocular diseases such as cataract/optic neuropathies and macular ischemia. Also, some of the patients included in the study had a chronic oedema with distortion / disintegration of the ellipsoid zone on OCT. This is an established unfavourable prognostic sign and therefore the patients’ vision did not improve despite an improvement in CRT achieved by the anti-VEGF injections.

Similarly, Kamei *et al.* conducted a 3-month study in Japanese patients with visual impairment due to macular oedema secondary to retinal vein occlusion (RVO).<sup>15</sup> The BCVA improved (12.8 and 9.1 letters) and the mean CRT decreased (212.5 and 442.1 μm) from baseline to month 3 for BRVO and CRVO respectively<sup>15</sup>, and these results were comparable to those of our study.

We also see that while the fall in CRT is significant, the decrease in macular volume was statistically insignificant. This may be due to inclusion of consecutive cases with macular oedema

of all severities. Similar to the results of the DRCR.net protocol T, the improvement seen in milder cases was less than the improvement seen in cases with more severe oedema.

In this study, we have used Ranibizumab recently being sold under the label of Patizra<sup>®</sup> and aimed to conduct the first on ground audit of the efficacy of this new product and compare it with Lucentis<sup>®</sup> results.

A major strength of our study was its prospective study design and the fact that it encompassed most of the common retinal pathologies that lead to macular oedema. In addition, the study was the first to provide real-life data in Pakistani patients on Patizra<sup>®</sup> and to establish its efficacy in treating various retinal disorders. We included treatment naïve patients only, and analyzed OCT parameters which are directly influenced by the effects of Patizra<sup>®</sup>, thereby providing an objective measure of efficacy. The analysis was limited, however, by lack of a control group and a limited sample size. Despite these limitations, our study supports the current data available regarding the short-term effectiveness of intravitreal ranibizumab (marketed under the label of Lucentis<sup>®</sup>) and proved that Patizra is as effective as Lucentis<sup>®</sup> in the management of macular oedema and producing positive visual outcomes. Further avenues of extended research on this topic will include more extended follow up than present, and comparison with other anti-VEGF molecules like Bevacizumab and Aflibercept.

## CONCLUSION

In conclusion, Patizra<sup>®</sup> significantly improves visual acuity and anatomical morphology in Pakistani patients with visual impairment due to macular oedema secondary to various retinal pathologies.

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## Conflicts of Interest:

The authors declare no conflicts of interest.

## AUTHORS' CONTRIBUTION

HAM, RS, MA: Data collection, conceptualization of study design, literature search, write-up. MA, MU: Data analysis and interpretation, write-up. HK, AA:

Interpretation of scans, data collection, critical review of write-up.

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## Address for Correspondence:

Hajra Arshad Malik, Research Assistant, Medical Retina Clinic, Amanat Eye Hospital, Islamabad-Pakistan

Email: hajra.arshad93@gmail.com