

### **Title : The Use of Razumab in the treatment of CNVM with Macular Edema**

#### **Presenting symptoms :**

A 56 year old female patient presented in the ophthalmology OPD with complaints of gradual onset diminution of vision in both eyes over the 10 months with sudden exacerbation in the left eye since last three weeks .

#### **Past History :**

The patient was a known case of Diabetes Mellitus for the last five years and has been on oral hypoglycaemics for the same.

#### **General examination findings :**

The patient was co-operative, oriented and well built. Her blood pressure was 110/80 mm Hg ,pulse rate was 89/min, respiratory rate was 22/ min. There were no abnormalities found on systemic examination.

#### **Local examination findings:**

Anterior segment examination revealed Immature senile cataract in both eyes. The fundus of right eye (RE) was within normal limit, while the left eye (LE) showed intraretinal haemorrhage just inferior to the macula, with surrounding oedema. The optic disc showed inferior gliosis. Other findings were clinically within normal limits.

**Symptoms:** The patient reported altered shapes of surrounding objects (metaphorhopsia) with the presence of dark circle periphery to the field of vision.

**Signs:** Juxta foveal intraretinal haemorrhage with macular oedema (LE)

#### **Laboratory Investigations:**

- Hb- 11 gm%
- WBC- 8,000 cells/ cumm
- Platelets- 200,000 / cumm
- ESR- 15
- Fasting blood sugar – 101 mg/dl
- Post prandial blood sugar- 128 mg/dl
- HBA1C- 7.5 %
- Serum creatinine – 1.5 mg/dl

#### **Specific Investigations:**

Best corrected Visual Acuity (BCVA) of RE was 6/18 and LE was 6/60. Fundus photo and Optical Coherence Tomography (OCT) showed intraretinal cystic spaces with thickened macula and para macular area with breach of the Bruch's membrane suggestive of Choroidal Neovascular Membrane (CNVM) in the left eye.

### **Diagnosis:**

A diagnosis of Parafoveal Choroidal neovascular membranes with macular oedema in the left eye, along with Immature Senile Cataract in both eyes.

### **Treatment :**

The patient was given Intravitreal Injection Razumab on three occasions , the first two given one month apart, and the third 8 months later, in the left eye. Green focal laser treatment was done at the parafoveal areas of CNVM once the macular oedema resolved.

### **Result :**

The patient showed considerable improvement after treatment . The pre-operative vision of 6/60 changed to 6/36, 6/18, 6/6p, post operatively. Progressive tests show gradual reduction in macular oedema along with resolution of the Bruch's breach.

### **Discussion**

#### ***Discussion:***

Age related macular degeneration (AMD) is a degenerative disease which usually occurs in patients who are at least 50 years old and above. The involvement of the macula can cause impaired vision which may progress to legal blindness because of atrophy or complications due to neovascularisation. There are mainly two distinct types of AMD; the dry form which is characterised by drusen or abnormalities of the retinal pigment epithelium (RPE) such as atrophy, or hypopigmentation or hyperpigmentation. The wet type , or the neovascular type is distinguished by choroidal neovascularisation (CNV). When the new vessels extend under the centre of the foveal avascular zone (subfoveal CNV), it can cause severe vision loss. They proliferate from the choriocapillaris and extend through Bruch's membrane, to invade the area under the RPE, leaking serous fluid, lipid or blood, into this space. This leads to the development of fibrous tissue which replaces the normal structure of the outer retina, which often leads to severe, irreversible central vision loss.

Macular oedema causes increased retinal thickness, which is a common complication of diabetic retinopathy causing proliferative retinal microangiopathy or diabetic retinopathy, DR<sup>3</sup>, neovascular AMD and other causes of CNV, leading to blindness.<sup>2</sup> Although neovascularisation is present in less than 20% of all patients with AMD, it is responsible for 90% of the cases with severe vision loss.<sup>1</sup> In developing countries like India, the elderly population is increasing which may explain the prevalence of AMD ranging from 3.1 to 10.6%, accounting for 1.7–3.3% of all cases of blindness diagnosed.<sup>5</sup>

Vascular endothelial growth factor (VEGF) is the cytokine that plays a role in the pathogenesis of CNV, causing increased permeability of the blood- retinal barrier. Anti-VEGF agents like Intravitreal ranibizumab has emerged as the primary standard treatment option for the treatment of retinal vascular diseases, due to its favourable outcome when compared

with the previous treatment options like thermal laser photocoagulation and photodynamic therapy (PDT) with intravenous verteporfin.<sup>6</sup>

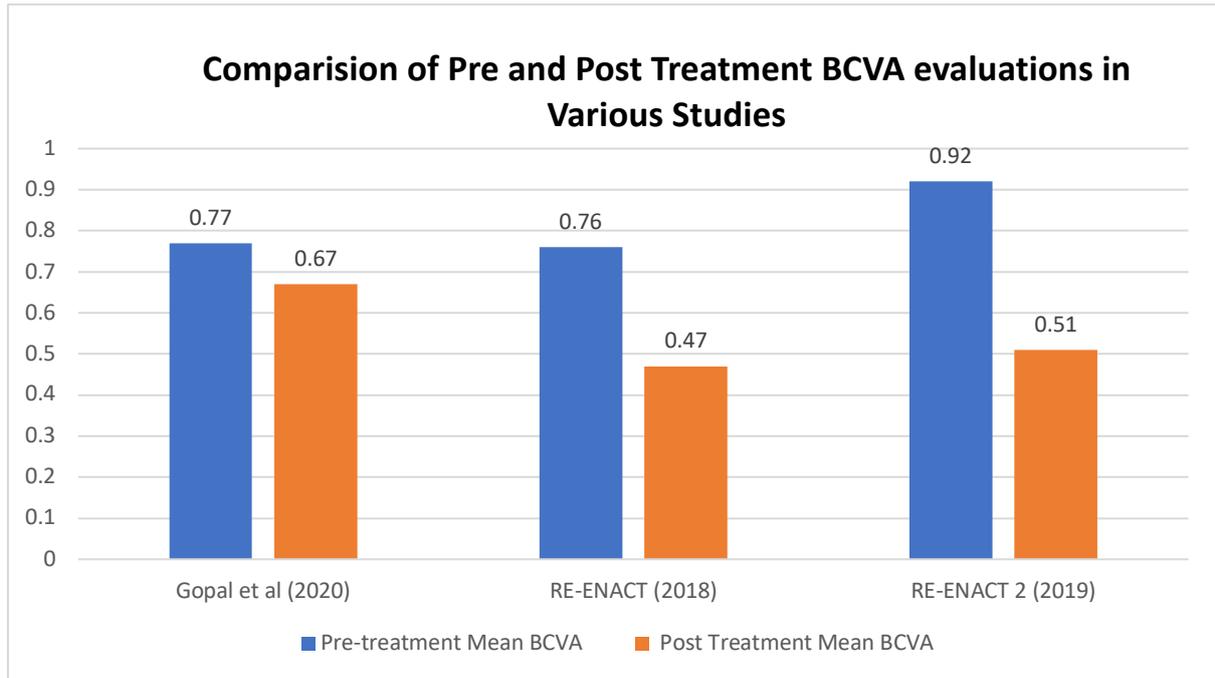
Initially , Ranibizumab was used as the anti- VEGF agent for the treatment of CNVM. However in 2015, the Drug Controller General of India approved Razumab® (the world's first biosimilar of ranibizumab by Intas Pharmaceuticals Ltd.) for the treatment of wet age-related macular degeneration (wet AMD), diabetic macular oedema (DME), macular oedema following renal vein occlusion and visual impairment due CNVM. <sup>4</sup> Razumab© mimics its biologic reference drug ranibizumab, which is a recombinant humanized monoclonal murine IgG1 antibody fragment that binds to all forms of VEGF.<sup>5</sup> Inhibition of the VEGF leads to decreased proliferation and permeability of the choroidal vessels, leading to decreased macular oedema and improved vision.

In a study conducted by Gopal S et al <sup>5</sup>, evaluated 309 eyes of 297 patients with retinal pathologies like wet AMD, diabetic macular edema (DME) and Retinal Vein Occlusion (RVO) with macular edema, who were treated with Razumab. Baseline Visual acuity assessments (BCVA) and measurement of Central Foveal Thickness (CFT) was done before initiation of treatment and repeated again one month after treatment with Razumab. The BCVA decreased from 0.77 Log MAR to 0.67 log MAR, while the CFT reduced from 377.59 µm to 303.58 µm after one month, indicating significant improvement in the disease condition.

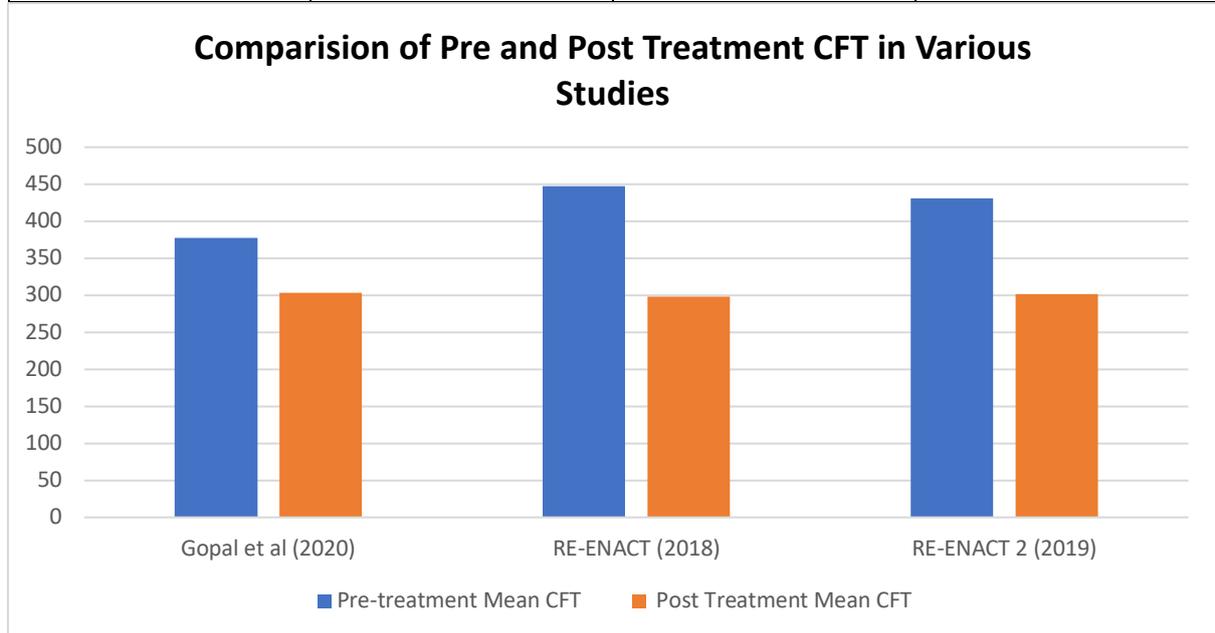
The RE-ENACT study ( The REal life assessmENT of safety And effeCTiveness) for Razumab conducted by Sharma et al<sup>4</sup>, in 2018, evaluated the effect of Razumab on patients with macular oedema due to retinal vein occlusion, and revealed improved BCVA from baseline (0.76 ± 0.04) to week 12 (0.47 ± 0.02; p < 0.0001), while the CFT significantly decreased from baseline (447.60 ± 10.91 µm) to week 12 (298.23 ± 6.68 µm; p < 0.0001).

A follow up, long term evaluation study by the same researchers, RE-ENACT 2,<sup>6</sup> conducted in 2019, examined the use of Razumab in wet age-related macular degeneration. Out of the 103 patients evaluated, 57.9% of the patients had received 3 doses of the injection, with a range of 1 to 5 injections. Significant improvements were observed from baseline to all timepoints with BCVA 0.92 ± 0.6 decreased to 0.51 ± 0.4 (P = 0.0014) while the CFT decreased from 430.83 ± 14.4 µm to 301.26 ± 11.6 µm (P = 0.0001), by week 48.

	<i>Pre-treatment Mean BCVA</i>	<i>Post Treatment Mean BCVA</i>	<i>P value</i>
<b>Gopal et al (2020)</b>	0.77 Log MAR	0.67 log MAR	-
<b>RE-ENACT (2018)</b>	0.76 ± 0.04	0.47 ± 0.02	P < 0.0001
<b>RE-ENACT 2 (2019)</b>	0.92 ± 0.6	0.51 ± 0.4	P = 0.0014



<b>Study</b>	<b>Pre-treatment Mean CFT</b>	<b>Post Treatment Mean CFT</b>	<b>P value</b>
<b>Gopal et al (2020)</b>	377.59 $\mu$ m	303.58 $\mu$ m	-
<b>RE-ENACT (2018)</b>	447.60 $\pm$ 10.91 $\mu$ m	298.23 $\pm$ 6.68 $\mu$ m	P < 0.0001
<b>RE-ENACT 2 (2019)</b>	430.83 $\pm$ 14.4 $\mu$ m	301.26 $\pm$ 11.6 $\mu$ m	P = 0.0001



**Conclusion**

Razumab is an effective treatment option for treating retinal pathologies causing macular oedema like CNVM, RVO and DME. This is demonstrated in the current case where the patient showed considerable improvement in post treatment vision, with a decrease in macular oedema.

## References

1. Soubrane G, Bressler NM. Treatment of subfoveal choroidal neovascularisation in age related macular degeneration: focus on clinical application of verteporfin photodynamic therapy *British Journal of Ophthalmology* 2001;85:483-495.
2. Bhende M, Shetty S, Parthasarathy MK, Ramya S. Optical coherence tomography: A guide to interpretation of common macular diseases. *Indian J Ophthalmol.* 2018;66(1):20-35.
3. Hua R, Li Q, Wong IY, Ning H, Wang H. Choroidal microvascular proliferation secondary to diabetes mellitus. *Oncotarget.* 2017;10;8(2):2034-2036.
4. Sharma S, Khan MA, Chaturvedi A; RE-ENACT Study Investigators Group. Real-Life Clinical Effectiveness of Razumab® (the World's First Biosimilar of Ranibizumab) in Retinal Vein Occlusion: A Subgroup Analysis of the Pooled Retrospective RE-ENACT Study. *Ophthalmologica.* 2019;241(1):24-31.
5. Gopal S, Kasturirangan S, Madhivanan N, Henderson H, Nivean P, Shekharan S. Clinical effectiveness and safety of Razumab (a biosimilar of ranibizumab) 2020; 58 (3): 154- 158
6. Sharma S, Khan M, Chaturvedi A; RE-ENACT 2 Study Investigators Group. A Multicentre, Retrospective Study (RE-ENACT 2) on the Use of Razumab™ (World's First Biosimilar Ranibizumab) in Wet Age-Related Macular Degeneration. *Ophthalmol Ther.* 2020;9(1):103-114.