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Analyse the Efficacy and Safety of Intravitreal Injection of Biosimilar Ranibizumab on Central Macular Thickness and Visual Outcome in Patients of Macular Edema

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Abstract: ***The biosimilarranibizumab like its biologic reference drug (Lucentis; Genentech) is a recombinant humanized IgG1 monoclonal antibody designed for intraocular use. Recombinant humanized IgG1 kappa isotype monoclonal antibody fragment, inhibits the biologic activity of humanVEGF-A. In this paper, efficacy of single intravitreal injection of biosimilarranibizumab on central macular thickness and visual outcome in patients of macular oedema with different retinaletiology is presented. Effect of biosimilar intravitrealranibizumab for DME, pseudo phakiccystoid macular edema and macular edema secondary to RVO was observed over period of 3 months with improvements in visual acuity and CFT without detectable ocular and systemic toxicity.***

Keywords: Intravit real biosimilar ranibizumab, central macular thickness, visual outcome

1. Introduction

Macular oedema is defined as an accumulation of fluid in the outer plexiform layer and the inner nuclear layer as well as a swelling of Muller cells of the retina.All pathological conditions leading to a breakdown of the BRB cause a retention of proteins within the retinal tissue, resulting in the development of oedema due to consecutive water retention by osmosis.

VEGF is one of the most important regulators of vasculogenesis and angiogenesis. Under pathological conditions, it plays a role in several ocular disorders such as diabetic retinopathy, age-related macular degeneration and retinal vascular occlusive diseases.

Drugs that inhibit the actions of vascular endothelial growth factor(VEGF)causes retinal disease by increasing leakage & thus using swelling & benefits patients by decreasing the abnormal & harmful new blood vessel formation & decreasing the leakage & swelling of retina, leading to stabilization of vision.

The biosimilarranibizumab like its biologic reference drug (Lucentis; Genentech) is a recombinant humanized IgG1 monoclonal antibody fragment designed for intraocular use.

Each mL contains 10 mg ranibizumab. Each vial contains 2.3 mg of ranibizumab in 0.23 mLsolution.

2. Aims and Objectives

1) To analyse the efficacy of single intravitreal injection of biosimilarranibizumab on central macular thickness and visual outcome in patients of macular oedema with different retinaletiology.
2) To analyse the safety of intravitreal injection of biosimilarranibizumab in patients of macular edema with different retinalpathology.

3. Material and Method

A prospective nonrandomized observational clinical study performed at tertiary eye care hospital starting from AUGUST 2017 to AUGUST 2019.

Sample size: 100

Inclusion Criteria
Patients having MACULAR EDEMA secondary to:
1) Diabetic MacularEdema
2) Retinal venousocclusion
3) Pseudo phakiccystoid macularedema

Exclusion Criteria
1) Patient previously treated with other INTRAVITREAL Anti VEGF/STEROID
2) Unstable metaboliccontrol
3) Raised Intra ocularpressure
4) Patient with active surfaceinfection

Post Injection Assesment

Follow up to be performed on the next day, 1 week, 1 month & 3 months post injection & will include the following parameters:
1) Visualacuity
2) Intra ocular pressure with applanationtonometry
3) SLE(anterior segment & 90 D examination for detailed macular evaluation)
4) Indirect ophthalmoscopy to look for the site ofinjection
5) OCT for assessment of central macular thickness to compare the pre & post injection macularstatus.
6) Fundusphoto

4. Observations and Results

A prospective nonrandomized observational clinical study was performed on 98 patients and 100 eyes at tertiary eye care hospital.

Table 1: Age Group

AGE	Number	Percent
25-45	8	8
45-65	14	14
65-85	76	76
TOTAL	98	100

Table 2: Gender Distribution:

Gender	Frequency	Percent
F	35	35.7
M	63	64.3
Total	98	100.0

Table 3: Diagnosis

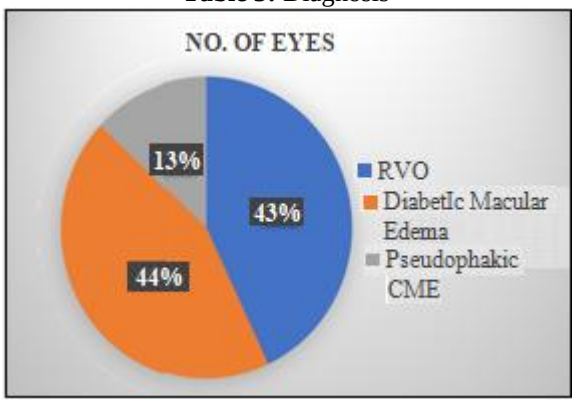

Table 4: Types

Diagnosis	*Types*	*No. of Eyes*	*Percentage*
RVO	CRVO	20	20
	BRVO	23	23
DME	CYSTOID	13	13
	CYSTOID –SPONGY	11	11
	SFSD	20	20
PSEUDO PHAKIC CME		13	13
TOTAL		100	100

P Value: It is calculated using Anova test which was <0.001 for number of eyes receiving IntravitrealBiosimilarRanibizumab for Retinal Venous Occlusion which included CRVO and BRVO,diabetic ME, aphakic or pseudophakic ME. This shows that vision improvement at the end of 3 months post injection remains statistically significant.

Table 5: Baseline V/S Post Injection Intra Ocular Pressure in mmHg analysis:

Diagnosis	Baseline	Post Injection				P Value
		Day 1	1 Week	1 Month	3 Months	
RVO	16.65 (±3.25)	16.7 (±3.05)	16.05 (±2.74)	16.19 (±2.82)	16.14 (±3.13)	0.4162
CRVO	15.75 (±3.24)	16.1 (±2.86)	15.3 (±2.92)	15.3 (±2.92)	15.2 (±2.63)	0.4253
BRVO	17.43 (±3.12)	17.22 (±3.18)	16.7 (±2.46)	16.96 (±3.18)	16.96 (±3.35)	0.8176
DME	16.57 (±3.11)	16.59 (±2.50)	16.14 (±2.87)	16 (±2.96)	16.41 (±2.50)	0.8268
CYSTOID	16.38 (±3.52)	16.77 (±2.39)	15.8 5(±2.76)	16.62 (±3.86)	17.54 (±2.18)	0.7939
Cystoidspongy	16.09 (±3.75)	17.09 (±3.02)	16.55 (±3.11)	16.36 (±2.80)	15.64 (±2.50)	0.907
SFSD	16.95 (±2.52)	16.2 (±2.33)	16.1 (±2.94)	15.4 (±2.35)	16.1 (±2.55)	0.5213
Pseudo Phakiccme	18.92 (±2.06)	16.46 (±3.67)	16.15 (±2.51)	16.46 (±2.33)	18.31 (±2.29)	0.138

Table 6: Post Injection Adverse Effects

Adverse Effects	*Frequency*	*Percentage*
SCH	14	14%
Pain	3	3%
Floaters	2	2%
No Adverse Effects	81	81%
Total	**100**	**100%**

5. Discussion

1) In our study were 43 patients with **RVO** of which 20 had CRVO & 23 had BRVO, who received intravitreal biosimilar ranibizumab, which showed a mean change in vision and central foveal thickness from 1.09(±0.32) to

0.59(±0.31) and 639.3(±233.67) to 321.26(±166.51) respectively showing rapid and sustainable improvement in visual acuity as well as central foveal thickness of the patient with no significant change in intraocular pressure with no significant adverse effect showing the efficacy and safety of thedrug.

2) "New developments in the classification, pathogenesis, risk factors, natural history and treatment of branch retinal venous occlusion" have concluded that anti-VEGF Ranibizumab (Reference drug) bring about significant improvement in visual acuity and central foveal thickness with relatively fewer complications, thereby revolutionizing the treatment of CME associated with BRVO which was comparable to ourstudy.
3) Intravitrealranibizumab anti- VEGF therapy(Reference drug) showed marked improvement in BCVA along with reduction in CMT in patients with retinal vein occlusion with no serious ocular or systemic complications showing results of intravitreal reference ranibizumab comparable to our study of intravitrealbiosimilarranibizumab.
4) Our study included 44 patients of **Diabetic Macular Edema** which included cystoid, cystic-spongy ad sub-foveal serous detachment type of edema, with improvement in mean visual acuity and central foveal thickness showing improvement in visual acuity and central foveal thickness from 1.24(±0.36) to 0.84(±O.33) and 700.66(±232.70) to 438.61(±212.45) 3 months post injection in all 3 types of edema with no significant change in intra ocular pressure and no systemic/local side effects showing safety and efficacy ofdrug.
5) In our study on 13 patients with **Pseudo-phakic CME** showed effective improvement in vision and central foveal thickness showing mean change in vision in logMAR from 0.88(±0.19) to 0.61(±0.20) and decrease in central foveal thickness in Microns from 478.77(±155.31) to 289.46(±103.92) with no significant adverse effects suggesting the safety and efficacy of thedrug.
6) Overall adverse effects noted among different patients were: subconjunctivalhaemorrhage in 14 patients, pain in 3 patients and floaters amongst 2 patients with no complains like redness or diminision of vision suggesting the safety of the drug.

6. Conclusion

1) Prospective, non-randomised study enrolling 100 eyes with macular edema secondary to different retinal etiology (Example RVO, DME, PCME) treated with single intravitreal injection of biosimilarranibizumab suggested that VEGF inhibition plays a key role in the treatment of macularedema.
2) The effect of biosimilarintravitrealranibizumab for DME, pseudo phakiccystoid macular edema and macular edema secondary to RVO was observed over a period of 3 months with improvements in visual acuity and CFT without detectable ocular and systemic toxicity.
3) The biosimilarRanibizumab proved to be effective treatment of macular edema secondary to Retinal vascular disorders in our study. The cost involved in intravitreal anti VEGF drug is high and in our population this may be a factor that patient is not willing for the treatment. Cost factor involved in intravitreal anti VEGF treatment is a biggest hurdle to treat these pathology in clinicalpractice.
4) The efficacy and safety of anti VEGF BiosimilarRanibizumab can overcome this and allow more patients tuefor treatment as it is cost effective.
5) The data showed good clinical response. The study in 100 eyes shows no evidence of acute adverse reaction and safety concerns.

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