Section: Ophthalmology

Original Research Article

A COMPARATIVE CROSS SECTIONAL STUDY ON EFFECT OF INTRAVITREAL RANIBIZUMAB VERSUS BROLICIZUMAB INJECTIONS IN nAMD (NEOVASCULAR AGE RELATED MACULAR DEGENERATION) AT A TERTIARY EYE CARE

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Received *: 10/01/2025*
Received in revised form *: 25/02/2025*
Accepted *: 13/03/2025*

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DOI: 10.70034/ijmedph.2025.1.269

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (1); 1435-1438

ABSTRACT

Background: To compare the safety and efficacy of ranibizumab and brolucizumab injections in both comparision groups diagnosed with neovascular age related macular degeneration (nAMD) at the end of 6 months from the onset of treatment.

Materials and Methods: A prospective cross sectional comparative study in patients attending retina out patient department ophthalmology 60 patients who meet the study criteria during the period of 18 months from the time of approval. Age >=50 in Active subfoveal choroidal neovascularization. All patients completed 6 months follow up. Therefore 60 eyes of 60 patients with a follow up period of 6 months were included in the analysis. 3 doses of injection given at interval of 1 month

Results: Our study has more number of males than females in ranibizumab group (group 1) and comparatively mild higher side on males than females in brolucizumab (group 2). In group 1 mean age was in years 62.35±7.87years In group 2 mean age was in years 58±5.1 years. In group 1 majority of patients are of age group 50-60 years In group 2 majority of patients are of age group 50-60 years. Best corrected visual acuity in who received Ranibizumab injection improved from baseline to till end of 6 months is significant. ($p<0.0001$) In AMD cases treated with Ranibizumab the foveal thickness improved from baseline to till end of 6 months is significant.

Conclusion: Intravitreal Ranibizumab and brolucizumab have almost similar visual outcome .Intravitreal brolucizumab is more effective in reducing foveal thickness showing better anatomical result compared with ranibizumab.

Keywords: Neovascular Age Related Macular Degeneration (nAMD), Ranibizumab, Brolicizumab.

INTRODUCTION

Age related macular degeneration also known as age related maculopathy is a slowly progressive degenerative disease with pathology centered principally in the macula lutea of retina. It leads to severely reduced central vision and over many years leads to decrease in quality of life as the disease progresses. Ninety percent of all people with AMD have the dry type, which includes the early and intermediate stages of AMD, as well as the advanced form known as geographic atrophy. The wet form affects 10 percent of all people with AMD and accounts for 90 percent of legal blindness from the disease.[1,2]

The presence of choroidal neovascular membrane is the hallmark feature. CNVM consists of buds of neovascular tissue and accompanying fibroblasts from choroid perforating bruch's membrane with extension either above or below the retinal pigment epithelium. These neovascular complexes are

associated with hemorrhages, fluid exudation, fibrosis formation resulting in photoreceptor damage and visual loss which is then treated with anti VEGF injections.

MATERIALS AND METHODS

A prospective cross sectional comparative study IN Patients attending Retina out patient department at Sarojini devi eye Hospital, Regional institute of ophthalmology, Hyderabad Telangana. 60 patients who meet the study criteria during the period of 18 months from the time of approval.

Inclusion Criteria: Age >=50 in Active subfoveal choroidal neovascularization

Exclusion Criteria: Previously treated for choroidal neovascularization, Presence of other retinal pathologies compromising visual acuity any contraindications for ranibizumab and brolucizumab, active intraocular and periocular infections in either eye, with evidence of other causes of CNVM such as myopic choroidal neovascularization, ocular histoplasmosis, angiod streaks, choroidal tears, ocular trauma, iatrogenic, inflammatory diseases of choroid and retina.

Patients presenting with sudden onset of diminution of vision painless progressive and those demonstrating drusens with CNVM changes in fundus in slit lamp biomicroscopy using 90D done, were further evaluated. A complete history, clinical work up,demographic data are collected. Initial best corrected visual acuity (BCVA)was recorded by Snellen's chart. Fundus fluorescein angiography (FFA) was done to classify the type of CNVM. Spectral domain optical coherence tomography (SD-OCT) was done to study the structural changes before commencement of treatment to know the anatomical changes. The patients are treated with appropriate intravitreal anti VEGF injections as per requirement.

Follow ups of these patients were done for 6 month and 3 doses of injection given at interval of 1 month. BCVA was tested by snellen's chart at every follow up, correlated with OCT.

RESULTS

Out of 65 patients, 3 patients receiving ranibizumab and 2 patients receiving brolucizumab were lost to follow up. So 60 patients completed 6 months follow up. Therefore 60 eyes of 60 patients with a follow up period of 6 months were included in the analysis. The data after statistical evaluation were presented as mean±SD. Our study has more number of males than females in ranibizumab group (group 1) and comparatively mild higher side on males than females in brolucizumab (group 2).

Table 1: Age Distribution

Age in years	Group 1(ranibizumab)n=30	Group 2 (brolucizumab)n=30
50-60	13	16
61-70	7	10
71-80	9	4
81-90	1	0
Gender		
Males	21	17
Females	9	13

In group 1 mean age was in years 62.35±7.87years In group 2 mean age was in years 58±5.1 years. In group 1 majority of patients are of age group 50-60 years In group 2 majority of patients are of age group 50-60 years.

Table 2: Visual Acuity in present study

Visual acuity in log MAR	Group 1 Intravitreal Ranibizumab n=30	P value (Intra group)	Group 2 Intravitreal Brolucizumab n=30	P value (intra group)
Base line	1.5066 ± 0.157	0.0001	1.6 ± 0.162	0.0001
POD-1	1.5066 ±0.157	0.0001	1.6 ± 0.162	0.0001
1 Week	1.346 ± 0.131	0.0001	1.43 ± 0.146	0.0001
1 Month	1.33 ± 0.128	0.0001	1.30 ± 0.136	0.0001
3 Months	1.09 ± 0.091	0.0001	1.096 ± 0.09	0.0001
6 Months	1.02 ± 0.089	0.0001	1.05 ± 0.08	0.0001

Best corrected visual acuity in who received Ranibizumab injection improved from baseline to till end of 6 months it is significant. ($p<0.0001$).

Table 3: Foveal Thickness in present study

Foveal Thickness in µ	Group 1 Intravitreal Ranibizumab n=30	P value (Intra group)	Group 2 Intravitreal Brolucizumab n=30	P value (intra group)
Base line	441 ± 69.35	0.0001	445 ± 69.92	0.0001
POD-1	430.3 ± 67.43	0.0001	426 ± 66.42	0.0001
1 Week	416.43 ± 64.93	0.0001	408 ± 61.76	0.0001
Month	374.33 ± 57.48	0.0001	362 ± 54.84	0.0001
3 Months	336.73 ± 51.11	0.0001	320 ± 48.64	0.0001
6 Months	329.7 ± 45.64	0.0001	302 ± 43.45	0.01

In AMD cases treated with Ranibizumab the foveal thickness improved from baseline to till end of 6 months is significant.

DISCUSSIONS

This study compared intravitreal ranibizumab and brolucizumab for treating neovascular age related macular degeneration where group 1 includes 30 patients who received ranibizumab and group 2 includes 30 patients who received brolucizumab injections. 3 doses of injection given at interval of 1 month and these patients were followed up for 6 months.

Demographic profile Our study has majority of males in ranibizumab group and brolucizumab group and majority of them belong to the age group of 50-60 years of age. In AMD cases of group 1 the mean BCVA has improved from 1.5066±0.157 log MAR from baseline to 1.33±0.128 at 1 month and to 1.09±0.091 at 3 months,1.02±0.089 at end of 6 months .This is related to the patients who received Ranibizumab injection. In MARINA trial[4] which has taken 716 patients who received monthly injections of ranibizumab(0.3mg or 0.5mg)or sham injections for 24 months. The primary end point was the proportion of the patients losing fewer than 15 letters from baseline acuity at 12 months. The outcome is as follows. Patients losing fewer than 15 letters at 12 months:95% treated group Vs 62% in sham group($p<0.0001$). Patients gaining more than 15 letters at 12 months 25% and 34% treated groups (0.3mg and 0.5mg respectively) Vs 5% controls.

Average chance in visual acuity:7 letters gained intreated groups Vs 10 letters lost in controls. In AMD cases treated with Intravitreal brolucizumab the baseline BCVA improved from 1.6 ± 0.162 to 1.30 ± 0.136 at 1 months and to 1.096±0.09 at 3 months and to 1.05 ± 0.08 at end of 6 months. In HAWK and HARRIER,[5] which is phase 3 multicentre trial of brolucizumab for nAMD are randomized to intravitreal brolucizumab 3mg and aflibercept 2mg. After loading 3 monthly injections, brolucizumab treated eyes received 12 weekly injections and aflibercept 8 weekly. At 48 weeks brloucizumab has non inferiority to aflibercept in BCVA change from (6.6(6mg) and 6.1(3mg)) letters with brolucizumab Vs +6.8 letters with aflibercept (HAWK) + 6.9(6mg) brolucizumab Vs +7.6 aflibercept letters (HARRIER) $p<0.001$ for each.

In AMD cases treated with Ranibizumab the foveal thickness improved from 441 ± 69.35 baseline to 374.33 ± 57.48 at 1 month,336.73 ± 51.117 at 3 months ,329.7 ± 45.64 at end of 6 months. PrONTO trial was prospective non randomized single center trial investigating the efficacy of intravitreal ranibizumab given monthly for 3 months followed by as an required. Patients were given 3 monthly consecutive injections with intravitreal ranibizumab (0.5mg) subsequently 3rd to 24 months patients were examined with OCT. By 3 months after the first injection mean increase of 10.8 letters $p<0.001$ and mean reduction of central retinal thickness 190µm $p<0.001$ for ranibizumab. In patients treated with brolucizumab the foveal thickness improved from baseline 445±69.92 to 362±54.84 at 1 month,320±48. 64 at 3 months, 302±43.45 at end of 6 months. A study conducted by Robert P Finger et al [6] on comparative efficacy of brolucizumab in treatment of wet AMD where brolucizumab (6mg q12w/q8w) is compared against all relevant Anti VEGF regimens. In this study 19 RCT were included NMA based case analysis brolucizumab with loaded phase demonstrated superior retinal thickness reduction to most comparators like ranibizumab (0.5mg q4w,year 1 mean difference -50.1 and year 2 mean difference -49.5).[7,8,9] In HAWK and HARRIER trail,[5] greater than 50% brolucizumab treated eyes were maintained on 12 weekly dosing. Greater subfield thickness reductions from baseline to 48 weeks were observed with brolucizumab 6mg in HAWK (LS mean-172µmVs -143µm) $p=0.001$, HARRIERS (LS mean -193µm Vs -143.9µm) $p<0.01$.

In both the groups, no significant adverse effects were reported, with subconjunctival hemorrhage being the most common adverse effect in both groups, followed by increased intraocular pressure and mild ocular inflammation. These observations are in line with the observations of Mojica et al. and Fung et al.[10,11] There were no reported cases of endophthalmitis in the ranibizumab group in the PIER study. According to the Fung et al,[12] the incidence of endophthalmitis after using intravitreal injections of bevacizumab was 0.01%. Endophthalmitis, lens injury or retinal detachment was not observed in any patient in our study.

The mean number of injections required in our study in the bevacizumab group (4.3) was less than the number required in the ranibizumab group (5.6). This finding is similar to that of Fung et al,[12] and this can probably be explained by the fact that bevacizumab is a full-length molecule with a longer half life as compared to the fragmented molecule of ranibizumab which has a shorter half life. Repeat injections were not required in 25.93% in ranibizumab group and 21% in bevacizumab group.

There are few reported studies comparing head on head the efficacies of ranibizumab and bevacizumab till the time this article was written. Landa et al,[13] and Rosenfeld et al,[14] in their retrospective reviews concluded that there is no significant difference in the efficacies of ranibizumab and bevacizumab. Fong et al,[15] in a comparative retrospective case series concluded that both ranibizumab and bevacizumab groups showed similar improvement and stability of vision over time. Subramanian et al,[16] in their prospective randomized double masked single center study over 6 months concluded that visual outcomes of bevacizumab in wet AMD appear to be no different from ranibizumab. Their study had a total of 20 patients. However, Chang et

al,[17] concluded otherwise. In their retrospective comparative study, they concluded that short-term effectiveness of ranibizumab treatment, as measured by incremental improvement in OCT parameters, was significantly greater than bevacizumab treatment.

Thus, from our present study we can conclude that both ranibizumab and bevacizumab are safe and efficacious treatment are well tolerated. Intravitreal Ranibizumab and brolucizumab have almost similar visual outcome. Intravitreal brolucizumab is more effective in reducing foveal thickness showing better anatomical result compared with ranibizumab.

CONCLUSION

The results of our study show that the intravitreal ranibizumab and brolucizumab are effective in improving visual acuity and decreasing foveal thickness in neovascular age related macular degeneration cases .Further both these injections are well tolerated. Intravitreal Ranibizumab and brolucizumab have almost similar visual outcome .Intravitreal brolucizumab is more effective in reducing foveal thickness showing better anatomical result compared with ranibizumab .There were no significant IOP raise and inflammatory response secondary to these injections.

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