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A Multicenter, Retrospective Study (RE-ENACT 2) on the use of Razumab™ (World's First Biosimilar Ranibizumab) in Wet AMD, DME, RVO and Myopic CNV

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Abstract

Objective: The effectiveness of Razumab™ (world's first biosimilar ranibizumab) in macular disorders was established in the RE-ENACT study. The current RE-ENACT 2 study was conducted to evaluate the effectiveness of biosimilar ranibizumab in macular disorders for a longer-term.

Methods: RE-ENACT 2 was a multicenter, retrospective data collection study. Data were collected from the medical records of adult patients who received biosimilar ranibizumab injections between July 2015 and February 2019 at multiple centers (17 centers) across India. The study comprised both the previously treated and treatment naive patients. Data were analyzed for improvements in: best corrected visual acuity (BCVA), central subfield thickness (CSFT), intraocular pressure (IOP), and proportions of patients having intraretinal fluid (IRF), subretinal fluid (SRF) from baseline at Weeks 4, 8, 12, 16, 20, 24, 30, 36 and 48.

Results: A total of 341 patients were included in this study. Majority of the patients were also suffering from hypertension (58.1%) and diabetes (15.8%). The disease indications comprised wet age-related macular degeneration (wet AMD, 30.2%, n=103), retinal vein occlusion (RVO, 29.6%, n=101), diabetic macular edema (DME, 30.2%, n=103) and myopic choroidal neovascularization (mCNV, 10%, n=34). Majority of the patients were men (60.1%) and were treatment naïve (73.6%); majority (59.2%) of the patients had received 3 (range 1-5) biosimilar ranibizumab injections. From baseline to all timepoints, significant improvements (P<0.001) were observed for BCVA (baseline: 0.89 ± 0.6; Week 48: 0.43 ± 0.3) and CSFT (baseline: 467.09 ± 159.6; Week 48: 296.56 ± 49.7). Minimal changes in IOP, though not significant, were observed (baseline: 14.92 ± 3.4; Week 48: 13.89 ± 2.2; P=0.4307). A decrease in proportions of patients having IRF and SRF was also observed. There were no new safety concerns reported.

Conclusion: The RE-ENACT 2 study further strengthens the data of biosimilar ranibizumab with improvements in visual acuity and disease outcomes observed for a longer follow-up duration up to 48 weeks in patients with wet age-related macular degeneration, diabetic macular edema, retinal vein occlusion and myopic choroidal neovascularization without any new safety issues.

Keywords: Razumab; Biosimilar ranibizumab; Wet AMD; DME; RVO; mCNV; Anti-VEGF

Introduction

Vascular Endothelial Growth Factor (VEGF) and its receptors play a major role in vascular angiogenesis that may lead to retinal ischemia-induced neovascularization in Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and choroidal vascular diseases such as wet Age-related Macular Degeneration (AMD) and myopic choroidal neovascularization (mCNV). Anti-VEGF agents play a crucial role in the treatment of several macular disorders [1,2].

Ranibizumab is a recombinant humanized monoclonal murine antigen-binding fragment (Fab) antibody that binds to all isoforms of VEGF, [3] and has been used extensively for the treatment of wet AMD, DME, RVO and mCNV [4-7]. Anti-VEGF agents are the current gold standard treatment in wet AMD, a leading cause of vision loss globally [8,9]. Intravitreal ranibizumab injection has shown efficacy and safety in the treatment of wet AMD and has been approved by the US FDA and EMEA [9,10] Ranibizumab inhibits VEGF expression and thus, associated neoangiogenesis, an important step in the pathogenesis of wet AMD [11,12]. Several studies have proven the safety and efficacy of ranibizumab in the treatment of DME that resulted in its regulatory approval as the first anti-VEGF agent for DME [5]. VEGF disrupts the blood–retinal barrier, stimulates vascular endothelial growth and increases vascular permeability in the pathogenesis of RVO [13]. Ranibizumab has shown efficacy and safety in the treatment of RVO and has been approved for the treatment of macular edema secondary to RVO [13]. Clinical studies have demonstrated the safety and efficacy of anti-VEGF therapy in treating CNV secondary to pathologic myopia, and anti-VEGF agents have been proposed as first-line therapy for mCNV. Ranibizumab is the first anti-VEGF therapy approved to treat patients with mCNV [14].

Razumab™, world's first biosimilar ranibizumab developed by Intas Pharmaceuticals Ltd., is a cost-effective alternative which is easily accessible to patients of macular disorders, and it was approved by the Drug Controller General of India in 2015 for the treatment of wet AMD, RVO, DME, and mCNV. Sameera et al. used biosimilar ranibizumab for over a month without any detectable ocular and systemic toxicity and showed improvements in best corrected visual acuity (BCVA) and central macular thickness (CMT) in patients with wet AMD, DME, and macular edema secondary to RVO, and thus demonstrating biosimilar ranibizumab as a safe and low-cost alternative [15]. Real-life clinical effectiveness of biosimilar ranibizumab for the treatment of wet AMD, DME and RVO was established in a previous retrospective, multicenter, observational, short-term (3-months) RE-ENACT study [16-18]. The current RE-ENACT 2 study was conducted to generate long-term data on the use of biosimilar ranibizumab in the real-world clinical setting.

Methods

Study design, population, endpoints and statistical considerations

The RE-ENACT 2 study design was more or less similar but with few changes (mentioned in the discussion section) to the RE-ENACT study design, which is published elsewhere [16-18]. In RE-ENACT 2 study, the medical records of adult patients of either sex, who received intravitreal biosimilar ranibizumab injections as per routine clinical care for the management of macular disorders between July 2015 and February 2019 at 17 centers across India, were analyzed. The study included both treatment naïve and patients previously treated with other anti-VEGF/steroids/combined treatment/laser treatment. Patients were excluded if assessment of optical coherence tomography (OCT) was not available (i.e., dense cataract). This current study was conducted after ethics committee approval and in accordance with the protocol and the principles of the Helsinki Declaration.

The study endpoints included from baseline to Weeks 4, 8, 12, 16, 20, 24, 30, 36, 48: improvement in the BCVA (measured by Snellen's chart or the logMAR chart), central subfield thickness (CSFT, measured by spectral-domain OCT [SD-OCT]) and intra ocular pressure (IOP). The decrease in proportion of patients with intraretinal fluid (IRF) and subretinal fluid (SRF), measured by SD-OCT, from baseline to each timepoint, was also evaluated. The BCVA and CSFT were analyzed using two-tailed paired t-test, and IRF and SRF using $\chi 2$ test. All statistical analyses were done using SAS® 9.4 or higher.

Results

Patients disposition and demographics

A total of 341 patients were analyzed, of which, 60.1% were men and majority (73.6%) were treatment naïve. The treatment indications included wet AMD (30.2%, n=103), RVO (29.6%, n=101), DME (30.2%, n=103) and mCNV (10%, n=34). A total of 3 biosimilar ranibizumab injections (range: 1-5 injections) were received by 59.2% patients. Majority of the patients had hypertension (58.1%) and diabetes (15.8%). The baseline BCVA, CSFT and IOP values were available in 308, 298 and 312 patients, respectively. Table 1 represents the patient disposition and baseline characteristics.

Parameters	**Biosimilar ranibizumab (N=341)**
Age, years (mean ± SD)	60.5 ± 11.9
Sex, n (%)	
Men	205 (60.1)
Women	136 (39.9)
Indication, n (%)	
Wet AMD	103 (30.2)
DME	103 (30.2)
RVO	101 (29.6)
mCNV	34 (10.0)
Eye treated, n (%)*	
Left	164 (48.1)
Right	177 (51.9)
Phakic vs. Pseudophakic eye, n (%)*	
Phakic eye	196 (57.5)
Pseudophakic eye	138 (40.5)
Treatment, n (%)*	
Treatment naïve	251 (73.6)

Previously treated	68 (19.9)
Baseline BCVA Score, [logMar], mean ± SD**	0.89 ± 0.6
Baseline CSFT, µm, mean ± SD**	467.09 ± 159.6
Baseline IOP, mmHg, mean ± SD**	14.92 ± 3.4
Baseline SRF*	
Present n (%)	210 (61.6)
Absent n (%)	89 (26.1)
Baseline IRF*	
Present n (%)	236 (69.2)
Absent n (%)	69 (20.2)

Note: *Data not available for: 7 patients for phakic vs. pseudophakic eye, 22 patients for treatment naïve vs. previously treated, 42 patients for baseline SRF, and 36 patients for baseline IRF. **Baseline scores for BCVA available in 308 patients, CSFT in 298 patients and IOP in 312 patients.

Abbreviations: BCVA: Best Corrected Visual Acuity; CSFT: Central Subfield Thickness; IRF: Intra-Retinal Fluid; DME: Diabetic Macular Edema; mCNV: myopic Choroidal Neovascularization; RVO: Retinal Vein Occlusion; SD: Standard Deviation; SRF: Sub-Retinal Fluid; wet AMD: wet Age-Related Macular Degeneration.

Table 1: Patient disposition and baseline characteristics.

Best corrected visual acuity: A significant improvement (P<0.001) in the BCVA was observed from baseline to all timepoints (baseline: 0.89 ± 0.596; Week 48: 0.43 ± 0.3) indicating improved visual acuity. A slight decrease in BCVA improvement was observed at Weeks 30 and 36 compared to previous weeks, though these improvements were significant from baseline; the improvement was again observed thereafter (Figure 1). A maximum of 5 injections were administered and the improvements were observed up to 48 weeks. Majority (59.2%) of the patients had received 3 biosimilar ranibizumab injections, and there was a significant improvement (P<0.001) in BCVA from baseline to all timepoints in these patients. The change in mean BCVA from baseline to all timepoints did not differ significantly when evaluated for treatment naïve vs. previously treated patients (Supplementary Table 1).

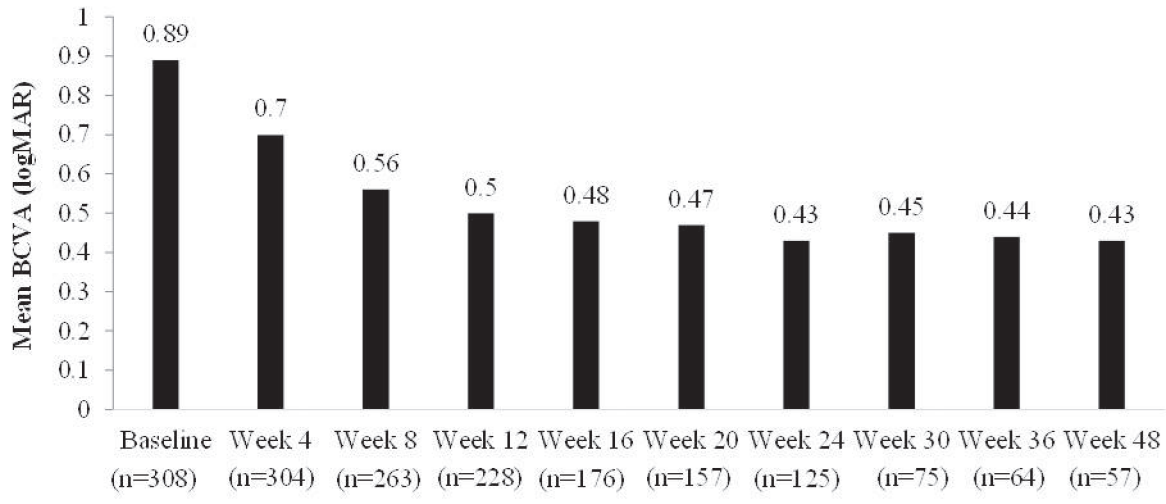

Figure 1: Mean BCVA at baseline and each timepoint after biosimilar ranibizumab administration. BCVA, best corrected visual acuity.

Central subfield thickness: A significant (P<0.001) decrease in CSFT scores indicating improved disease condition was observed from baseline to 48 weeks (baseline: 467.09 ± 159.6; Week 48: 296.56 ± 49.7) (Figure 2). Improvements in CSFT were continuous till the 20th week, after which, a slight decrease in the improvement was observed as compared with the previous weeks; however the improvements remained significant from baseline. There were significant improvements (P<0.001) in CSFT from baseline to all timepoints in

patients who received 3 biosimilar ranibizumab injections. The change in mean CSFT from baseline to all timepoints did not differ significantly when evaluated for treatment naïve vs. previously treated patients (Supplementary Table 2).

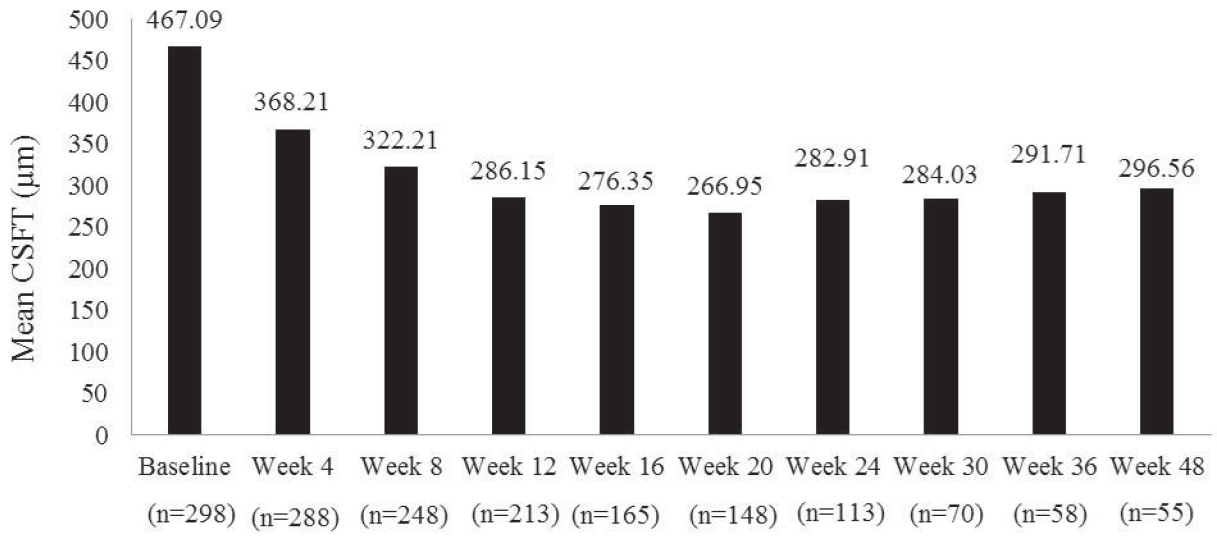

Figure 2: Mean CSFT (µm) at baseline and each timepoint after biosimilar ranibizumab administration. CSFT, central subfield thickness.

Intra ocular pressure, intraretinal fluid and subretinal fluid: The changes in mean IOP scores observed from baseline to 48 weeks (14.92 ± 3.4; 13.89 ± 2.2) were ± 1 mmHg at most of the timepoints and the changes were not significant. Similarly, the changes were not significant from baseline to all timepoints in patients who received 3 biosimilar ranibizumab injections. When evaluated for treatment naïve vs. previously treated patients, the changes in mean IOP from baseline to all timepoints were minimal and did not differ significantly. A significant ($P<0.05$) reduction in the proportion of patients having IRF or SRF from baseline to all timepoints was observed, indicating improved disease condition.

Discussion

Ranibizumab is an efficient treatment option with proven safety profile for various ocular disorders like wet AMD, DME, RVO and mCNV [19]. Several multi-center, randomized, prospective, controlled studies have confirmed the efficacy and tolerability of ranibizumab for various macular disorders. The high cost of innovator ranibizumab is a concern and ranibizumab is not affordable to many patients in developing countries such as India [15]. Razumab™, world's first biosimilar ranibizumab was developed by Intas Pharmaceuticals Ltd., to provide a cost-effective alternative (up to 25%) and easy accessibility of ranibizumab to patients of macular disorders [20]. The biosimilar ranibizumab is being used by leading ophthalmologists in India and has demonstrated effectiveness and safety for macular disorders in prospective and retrospective studies in Indian patients [15-18].

The real-world clinical practice has reported suboptimal treatment outcomes with innovator ranibizumab as compared to that reported in controlled clinical trials [21,22]. There is a scarcity of pooled data of different indications such as wet AMD, DME, RVO and mCNV in the public domain. A previous retrospective, observational data collection study 'RE-ENACT' (n=561) evaluated the 'real-world' clinical effectiveness of biosimilar ranibizumab, and demonstrated improvements in visual acuity and decrease in macular thickness [16]. The RE-ENACT study showed significant improvements in BCVA, CMT, IRF and SRF with the use of biosimilar ranibizumab injections (3 injections) in wet AMD, DME and RVO patients for a short-term (12 weeks) duration.

There is a requirement of long-term treatment in these chronic macular disorders with some studies having evaluated anti-VEGF treatments up to 5 years [23]. The RE-ENACT study had a short-term treatment and follow-up period of 12 weeks; hence, the current RE-ENACT 2 study was conducted to establish the 'real-world' effectiveness of biosimilar ranibizumab with a long-term treatment and follow-up duration of up to 48 weeks in a pool of patients with wet AMD, DME, RVO and additionally in patients with mCNV. This article presents the data on pooled indications while subgroup data for individual indications are planned to be published separately.

The effectiveness of biosimilar ranibizumab was measured by improvements in BCVA, CSFT, IRF and SRF in the current RE-ENACT 2 study, which demonstrated significant improvements in visual acuity (as measured by BCVA) and decrease in the macular thickness (as measured by CSFT) along with insignificant changes in IOP and decrease in proportion of patients with IRF and SRF for a longer follow-up duration (up to 48 weeks) in this pooled analysis of patients with wet AMD, DME, RVO and mCNV. Similar results with improved visual acuity (BCVA), macular thickness (CMT) and decrease in proportion of patients with IRF and SRF were reported with biosimilar ranibizumab in previous RE-ENACT study (12 weeks follow-up) in wet AMD, DME and RVO patients [16]. A prospective study also demonstrated improvements in BCVA (baseline: 0.67 ± 0.4; 1 month: 0.57 ± 0.4; P=0.001) and CMT (baseline: 345.9 ± 128.8 µm; 1 month: 287.66 ± 90.3 µm; P=0.001) with biosimilar ranibizumab in a pool of patients with wet AMD, DME and RVO [15].

Patients in the RE-ENACT study received 3 biosimilar ranibizumab injections but in the RE-ENACT 2 study, patients received 1 to 5

biosimilar ranibizumab injections overall. The pooled results from RE-ENACT study showed improvement in the visual acuity starting after the 1st biosimilar ranibizumab injection, which was maintained throughout the study period. The RE-ENACT 2 study also showed similar improvements in BCVA starting after the 1st injection, which was maintained throughout the 48-week study period.

The study limitations included its retrospective nature. Furthermore, the complete information on adverse events was not captured in the medical records, thus, not used in the analysis. However, there were no significant adverse events observed as compared with the innovator ranibizumab. This study measured the visual acuity with logMAR BCVA/Snellen's charts, which is considered inferior to the Early Treatment Diabetic Retinopathy Study (ETDRS) charts, used commonly in controlled clinical studies [24].

Conclusion

The RE-EANCT 2 study reinforces Razumab™, the world's first biosimilar of ranibizumab, as an effective treatment option in managing several macular disorders like wet AMD, DME, RVO and mCNV by reducing macular thickness and improving visual acuity.

This long-term RE-ENACT 2 study provides a clear picture about the effectiveness of the biosimilar ranibizumab in the real-world setting with effects of biosimilar ranibizumab seen as early as after the first injection with improvements lasting up to 48 weeks.

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Author Disclosure Statement

Drs. Shashikant Sharma, Mujtaba Khan, and Alok Chaturvedi are employees of Intas Pharmaceuticals Ltd, Ahmedabad. RE-ENACT 2 Study Investigator Group received an honorarium from Intas Pharmaceuticals Ltd. for their patient data contribution.

References

1. Penn JS, Madan A, Caldwell RB, Bartoli M, Caldwell RW, et al. (2008) Vascular endothelial growth factor in eye disease. Prog Retin Eye Res 27: 331-371.
2. Keane PA, Sadda SR (2012) Development of anti-VEGF therapies for intraocular use: A guide for clinicians. J Ophthalmol 2012: 483034.
3. Kim R (2007) Introduction, mechanism of action and rationale for anti-vascular endothelial growth factor drugs in age-related macular degeneration. Indian Journal of Ophthalmology 55: 413-415.
4. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, et al. (2006) Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 355: 1419-1431.
5. Dervenis N, Mikropoulou AM, Tranos P, Dervenis P (2017) Ranibizumab in the treatment of diabetic macular edema: A review of the current status, unmet needs, and emerging challenges. Adv Ther 34: 1270-1282.
6. Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, et al. (2010) Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 117: 1124-1133.e.

7. Hu Q, Li H, Du Y, He J (2019) Comparison of intravitreal bevacizumab and ranibizumab used for myopic choroidal neovascularization: A PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. Medicine 98: e14905.
8. García Layana A, Figueroa MS, Arias L, Araiz J, Ruiz Moreno JM, et al. (2015) Individualized therapy with ranibizumab in wet age-related macular degeneration. J Ophthalmol 2015: 412903.
9. Danyliv A, Glanville J, McCool R, Ferreira A, Skelly A, et al. (2017) The clinical effectiveness of ranibizumab treat and extend regimen in nAMD: Systematic review and network meta-analysis. Adv Ther 34: 611-619.
10. Qi HJ, Li XX, Zhang JY, Zhao MW (2017) Efficacy and safety of ranibizumab for wet age-related macular degeneration in Chinese patients. Int J Ophthalmol 10: 91-97.
11. Chong V (2016) Ranibizumab for the treatment of wet AMD: A summary of real-world studies. Eye 30: 270-286.
12. Ferro Desideri L, Barra F, Ferrero S, Traverso CE, Nicolo M (2019) Clinical efficacy and safety of ranibizumab in the treatment of wet age-related macular degeneration. Expert Opin Biol Ther 19: 735-751.
13. Gerding H, Mones J, Tadayoni R, Boscia F, Pearce I, et al. (2015) Ranibizumab in retinal vein occlusion: Treatment recommendations by an expert panel. Br J Ophthalmol 99: 297-304.
14. Zhang Y, Han Q, Ru Y, Bo Q, Wei RH (2015) Anti-VEGF treatment for myopic choroid neovascularization: From molecular characterization to update on clinical application. Drug Des Devel Ther 9: 3413-3421.
15. Sameera VV, Ayachit A, Joshi S, Guruprasad AS (2016) Safety and efficacy of razumab-the new biosimilar in india: Our experience. Kerala J Ophthalmol 28: 180.
16. Sharma S, RE-ENACT Study Investigators Group, Khan MA, Chaturvedi A (2018) Real life clinical effectiveness of razumab® (World's First Biosimilar Ranibizumab) in wet age related macular degeneration, diabetic macular edema, and retinal vein occlusion: A retrospective pooled analysis. Int J Ophthalmol Eye Res 6: 377-383.
17. Sharma S, Khan MA, Chaturvedi A, RE-ENACT Study Investigators Group (2019) 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 241: 24-31.
18. Sharma S, RE-ENACT Study Investigators Group, Khan MA, Chaturvedi A (2018) Real life clinical effectiveness of razumab® (World's First Biosimilar Ranibizumab) in wet age related macular degeneration: A subgroup analysis of pooled retrospective RE-ENACT study. Int J Ophthalmol Eye Res 6: 368-373.
19. Triantafylla M, Massa HF, Dardabounis D, Gatzioufas Z, Kozobolis V, et al. (2014) Ranibizumab for the treatment of degenerative ocular conditions. Clinical Ophthalmology 8: 1187.
20. Intas Pharmaceuticals Limited. Intas Launches RAZUMAB, Globally the First Biosimilar to Lucentis® (Ranibizumab). June19, 2015
21. Harrison L (2016) Real-World Anti-VEGF Data Disappointing. Medscape. Aug 11, 2016.
22. Harrison L (2017) Real world anti VEGF results fall short in macular edema. Medscape. Aug 13, 2017.
23. Wecker T, Ehlken C, Bühler A, Lange C, Agostini H, et al. (2017) Five-year visual acuity outcomes and injection patterns in patients with pro re-nata treatments for AMD, DME, RVO and myopic CNV. British J Ophthalmol 101: 353-359.
24. Kaiser PK (2009) Prospective evaluation of visual acuity assessment: A comparison of snellen versus ETDRS charts in clinical practice (An AOS Thesis). Trans Am Ophthalmol Soc 107: 311-324.