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Original Article

Ophthalmology Section

Comparison of Long-term Efficacy of Intravitreal Ranibizumab in Diabetic Retinopathy following Monthly vs Pro Re Nata vs Treat and Extend Protocol

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ABSTRACT

Introduction: Diabetic Retinopathy (DR) is a major complication of Diabetes Mellitus (DM), which remains a leading cause of visual loss in working age populations. The most common cause of vision loss in patients with DR is Diabetic Macular Oedema (DME). Intravitreal administration of anti-Vascular Endothelial Growth Factor (anti-VEGF) agents is currently the mainstay of therapy for both early and advanced stages of DR.

Aim: To compare long-term change in Central Macular Thickness (CMT) and Best Corrected Visual Acuity (BCVA) in patients with Non Proliferative Diabetic Retinopathy (NPDR) with Clinically Significant Macular Oedema (CSME) after receiving Intravitreal Ranibizumab (IVR) following monthly, Pro Re Nata (PRN) protocol and Treat and Extend (T&E) protocol.

Materials and Methods: This is a hospital based longitudinal prospective cohort study conducted on patients attending the Out Patient Department (OPD) of the Opthalmology Department at Midnapore Medical College and Hospital, West Bengal, India. from October 2018 to February 2021. Institutional Ethical clearance was obtained prior to the initiation of the study. Among 93 patients, 31 were chosen each for IVR PRN Monthly (Group A), (Group B) and T&E protocol (Group C) over a period of nine months. CMT and BCVA were measured at baseline and followed-up monthly for 12 months after last injection using Spectral Domain Optical Coherence Tomography (SD-OCT), while Glycated Haemoglobin (HbA1c) level was maintained below 7.4. Statistical analyses were performed using Statistical Package of Social Sciences (SPSS) statistics version 20 software. Chi-square test was used to find out the association between categorical variables. Pre and post comparisons were done using Wilcoxon sign rank test. A p-value less than 0.05 were considered as statistically significant.

Results: There was significant decrease in CMT and betterment of BCVA in all groups at the end of treatment compared to baseline. At six months and one year of last injection there was no significant change in CMT in group A and C while group B at one year (p=0.0487) showed significant increase. There was no significant worsening of BCVA in group A and group C while group B (p=0.01) showed significant worsening at one year long-term follow-up.

Conclusion: Thus, the present study concludes that, even though monthly protocol T&E protocol are equally good compared to PRN protocol on the basis of long-term beneficial effect, T&E protocol needed comparatively fewer doses of IVR compared to monthly protocol making it the choice of protocol for long-term control in NPDR with DME patients.

Keywords: Diabetic macular oedema, Glycosylated haemoglobin, Optical coherence tomography, Vascular endothelial growth factor

INTRODUCTION

Diabetic Retinopathy is a major complication of DM, which remains a leading cause of visual loss in working age populations. The diagnosis of DR is made by clinical manifestations of vascular abnormalities in the retina. Clinically, DR is divided into two stages: NPDR and Proliferative Diabetic Retinopathy (PDR). The most common cause of vision loss in patients with DR is DME. DME is characterised by swelling or thickening of the macula due to sub-retinal and intraretinal accumulation of fluid in the macula triggered by the breakdown of the Blood-Retinal Barrier (BRB) [1]. DME can occur at any stage of DR and cause distortion of visual images and a decrease in visual acuity. Current treatment strategies for DR aim at managing the microvascular complications, including intravitreal pharmacologic agents, laser photocoagulation and vitreous surgery. Intravitreal administration of anti-VEGF agents is currently the mainstay of therapy for both early and advanced stages of DR [2].

The IVR injection has been approved for the treatment of macular oedema following DME in 2015 [3]. There have been various protocols widely accepted in the IVR therapy worldwide, namely Monthly protocol, PRN protocol and T&E protocol. In monthly protocol, monthly administration of IVR is used until the disease activity terminates. While in PRN protocol, after three initial doses of monthly IVR the therapy is readministered only when the disease requires retreatment detected during monthly follow-ups. In T&E protocol initially the IVR therapy is continued till the macula goes dry and then the monthly follow-up schedules are deferred for definite interval usually for two weeks for decreasing hospital visits of the patient and IVR therapy is administered as per need [4].

Previous studies have shown reduced Glycosylated haemoglobin (HbA1c) level has a significant positive correlation with resolution of DME [4,5]. But according to the best knowledge, this study is first of its type where all the protocols have been compared together for their efficacy in maintaining long-term effect of IVR therapy in DR patients. Hence the objective of the study was to compare long-term change in CMT, BCVA in patients NPDR with CSME after receiving IVR following monthly, PRN protocol and T&E protocol, keeping adequate HbA1c control (HbA1c <7.4).

MATERIALS AND METHODS

The study design was a longitudinal prospective cohort study. It included the final diagnosis codes E11.311 encompassing Type 2 DM with unspecified DR with macular oedema according to the

International Classification of Diseases, Tenth Revision (ICD-10), on patients attending Ophthalmology Department at Midnapore Medical College and Hospital, West Bengal, India. The hospital-based study was performed from October 2018 to February 2021.

The protocol of the study followed the provisions of the Declaration of Helsinki. It was approved by the Local Bioethics Committee at the Midnapore Medical College as a quality assurance project (Reference number-IEC/21/06).

Inclusion criteria: Any patient over 18 years of age coming to the department with diagnosis of Type 2 DM with NPDR and DME requiring IVR without any retinal disease or significant cataract and willing to take part in the study was included in the study.

Based on the incidence of the disease and the attendance of DR patients in the institution, 93 patients of NPDR with CSME were included in the study.

Exclusion criteria: Patients who received previous intravitreal injections of anti-VEGF medications or corticosteroids within the previous 12 weeks or had any previous focal macular laser photocoagulation treatment were excluded prior to grouping.

Study Procedure

An informed consent was obtained from the patients prior to the study. They were well informed about the complete process of the study with possible risks and hazards.

Visual acuity of the patients was recorded at baseline and on subsequent follow-ups using Snellen's Chart and then converted to LogMar equivalent for analysis purpose. Detailed anterior segment and fundus examination was performed using Slit lamp with +90D Double Aspheric Lens [6,7].

Then all the patients underwent baseline CMT measurement to confirm the diagnosis of CSME using a Special Domain-Optical Coherence Tomography (SD-OCT) machine. HbA1c was measured at baseline and then at every three months till conclusion of the follow-up period.

All the patients were divided into three groups (A, B and C) of 31 patients each using systemic random sampling.

- Group A was posted for receiving monthly dosing IVR 0.5 mg for consecutive nine months or till the DME resolves whichever is earlier.
- Group B was posted to be given the same according to PRN Protocol.
- Group C received T&E protocol.

The group receiving IVR according to PRN protocol, after receiving initial three monthly doses, was followed by four weekly assessments in which retreatment was given as and when required if visual acuity dropped by 10 or more letters from baseline, if OCT central subfield thickness was greater than 250 μm, or if DME was judged to be the cause of visual acuity loss [8].

In T&E protocol, injection Ranibizumab was given till macula was dry. Then the next treatment was given at an increment of two weeks of each visit if the macula remained dry and a decrement of two weeks of each visit if there was new subretinal or intraretinal fluid on OCT [9].

Subsequent CMT and visual acuity was measured on each monthly follow-up for one year after last injection. Patients receiving retreatment with in the follow-up period by the means of additional intravitreal anti-VEGF injections or laser therapy were excluded from the study. Any patient not being able to maintain proper diabetic control assessed by HbA1c >7.4 were also excluded even if not requiring retreatment. Submitted scans were assessed for signal strength and image centration. Scans with signal strength below five or visibly decentred, if any, were excluded from the analysis. Finally group A had 26 patients, group B had 23 patients and group C had 25 patients each.

The primary outcome measured was change in mean CMT from baseline (at end of IVR therapy for nine months) and at six months after the last injection and one year of the last injection. Secondary outcome measures included comparison of mean change in BCVA and average number of intravitreal injections in all the protocols.

Every patient received 0.5 mg of IVR (Accentrix®; manufactured in India by Novartis) intravitreally for the treatment purpose. All the injections were given following adequate aseptic measures in the Ophthalmology Operation Theatre (OT). After dressing and draping, with the help of callipers the exact area of injection site was located at the pars plana region depending upon the phakic status of the patient. Then 0.5 mg of IVR was introduced intravitreally with the help of a 30G needle directed towards the centre of the globe. After delivering the adequate dose of IVR the needle was withdrawn carefully and the injection site was supported by a cotton pellet for a minute. Lastly, the eye was closed after instillation of 0.2 mL preservative free moxifloxacin eye drop at the site of injection. No serious postoperative complication was noted in any of the patients.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS Statistics version 20 software (IBM Corp., Armonk, NY, USA). Results of descriptive analyses were expressed as means±standard deviations for quantitative variables, and as counts and percentages for categorical variables. A Chi-square test was used to find out the association between categorical variables. Pre and post comparisons were done using Wilcoxon sign rank test. Intergroup variability of outcome was compared using F test for equal variances. A p-value less than 0.05 was considered as statistically significant.

RESULTS

A total of 93 patients with NPDR of different grades with CSME were enrolled randomly in the present study. The basic characteristics of the study population have been described in [Table/Fig-1].

Variables	Group A (n=26)	Group B (n=23)	Group C (n=25)	p-value
Age (Years)	49.46±7.76	54.88±8.54	50.52±7.29	0.94#
Gender (Male: Female)	18:08	14:09	15:10	0.03*
Laterality (RE: LE)	14:12	13:10	13:12	0.58*
Grade of NPDR (Number, %)				
Moderate	6 (23.1%)	7 (30.4%)	10 (40.0%)	
Severe	12 (46.1%)	9 (39.1%)	10 (40.0%)	
Very severe	8 (30.8%)	7 (30.4%)	5 (20.0%)	
Baseline CMT (μm)	536.78±111.7	520.67±86.27	534.58±111.89	0.46#
Baseline BCVA (LogMAR)	1.25±0.66	1.21±0.76	1.28±0.28	0.55#
Average No. of injections	7±1.68	6.35±1.13	5.28±1.34	0.09#

[Table/Fig-1]: Table showing basic characteristics of the study population divided into the 3 groups.
"*" Statistical significance (p-value) is measured using chi-square test.
"#" Statistical significance (p-value) is measured using Anova test formula; RE: Right eye; LE: Left eye

After end of treatment, all the patients were adequately controlled for HbA1c (HbA1c <7.4) level for next one year. During this period five patients from group A, eight from group B and six from group C were unable to maintain HbA1c (HbA1c <7.4) level at any point or needed retreatment due to re-appearance of oedema. These patients were excluded from the study. So, the final calculations reflect results on 74 individuals.

In this study, there was significant decrease in CMT in all three groups at the end of treatment compared to baseline (p<0.01). On subsequent follow-up at six months there was no significant change in CMT noted in group A, B and C signifying good short-term control. At one year long-term follow-up, all three groups show increased CMT from end of treatment, though non significant, while group B showed maximum increment which was statistically

significant (p=0.0487). None of the patients from group A and C required retreatment afterwards on follow-up due to good visual acuity maintenance and not meeting retreatment criteria while six patients from group B required retreatment meeting up the criteria after one year of last injection [Table/Fig-2].

Variables	Group A (n=26)	Group B (n=23)	Group C (n=25)
Baseline CMT (µm)	536.78±111.7	520.67±86.27	534.58±111.89
Average CMT at end of treatment (µm)	234.63±33.11	249.65±27.24	259.4±25.99
Average CMT at six months of follow-up (µm)	236.96±26.15	269.7±24.21	261.68±32.23
Average CMT at one year of follow-up (µm)	249.81±26.49	273.74±28.6	274.48±31.43
Significance of change in CMT from Baseline to end of treatment (p-value)*	<0.01	<0.01	<0.01
Significance of change in CMT from end of treatment to six month follow-up (p-value)*	0.64	0.07	0.69
Significance of change in CMT from end of treatment to one year follow-up (p-value)*	0.09	0.0487	0.09

[Table/Fig-2]: Table showing mean CMT and changes in CMT at the end of treatment, at 6 months and 1 year of follow-up in the 3 groups.
"*" Statistical significance (p-value) is measured using Wilcoxon sign rank test

In the present study, there was significant betterment of BCVA in all three groups at the end of treatment compared to baseline. On subsequent follow-up at six months there was no significant worsening of BCVA noted in group A, group B and group C. At one year long-term follow-up, all three groups showed BCVA worsening from end of treatment, of which Group B (p=0.01) showed statistical significance [Table/Fig-3].

Variables	Group A (n=26)	Group B (n=23)	Group C (n=25)
Baseline BCVA (LogMAR)	1.25±0.66	1.21±0.76	1.28±0.28
Average BCVA at end of treatment (LogMAR)	0.37±0.29	0.51±0.42	0.54±0.43
Average BCVA at six month follow-up (LogMAR)	0.44±0.23	0.6±0.29	0.64±0.28
Average BCVA at one year follow-up (LogMAR)	0.45±0.22	0.73±0.3	0.63±0.25
Significance of Change in BCVA from Baseline to end of treatment (p-value)*	<0.01	<0.01	<0.01
Significance of Change in BCVA from end of treatment to six-month follow-up (p-value)*	0.12	0.09	0.09
Significance of Change in BCVA from end of treatment to one year follow-up (p-value)*	0.09	0.01	0.08

[Table/Fig-3]: Showing mean BCVA and statistical significance of changes in BCVA at the end of treatment, at six months and one year of follow-up in the three groups.
"*" Statistical significance (p-value) is measured using Wilcoxon sign rank test

While comparing intergroup control of CMT and maintenance of BCVA it has been seen that group A and group C had no statistically significant difference between them with respect to control of CMT and maintenance of BCVA in one year long-term follow-up.

But statistically group A and group C both were superior to group B in terms of control of BCVA (A vs B: p=0.04; C vs B: p=0.04). On intergroup comparison of CMT, group B and C and A and B, non significant results were obtained [Table/Fig-4].

Parameters	A vs B	B vs C	A vs C
Significance of change in CMT from end of treatment to one year follow-up (p-value)*	0.28	0.28	0.49
Significance of change in BCVA from end of treatment to one year follow-up (p-value)*	0.04	0.04	0.5

[Table/Fig-4]: Intergroup comparison of Change in CMT and BCVA from end of treatment to 1 year follow-up.
"*" Statistical significance (p-value) is measured using F test for two sample variances

DISCUSSION

The recommended dose of DME for Ranibizumab is 0.5 mg (0.05 mL) administered once a month by an intravitreal injection. The phase III RISE and RIDE clinical trials and the phase III VIVID and VISTA trials established the superiority of anti-VEGF drugs over focal laser for the treatment of eyes with DME [9]. For eyes with centre-involving DME, monthly treatment leads to rapid visual acuity improvement that is maintained for at least three years. As and when needed (PRN) treatment protocol injections are administered based on the presence of DME compared to monthly injection protocol. The decision of treatment depends on factors such as changes in visual acuity or persistent or worsening centre-involving DME on clinical examination or Optical Coherence Tomography (OCT) imaging. A T&E regimen inherits qualities of both monthly and PRN treatment regimens [4]. Here, instead of a fixed four week follow-up interval, the length of the interval varied based on disease activity. The treatment interval was extended by one to two weeks at a time on controlling the DME, as long as vision and macular oedema remain stable. If macular oedema recurs or the visual acuity decreases, the interval was shortened by one to two weeks until the eyes return to their baseline [10].

In this study, all the groups had mean age of the patients in a comparable range >49 years with male preponderance. There was no bias over laterality. Baseline CMT and baseline BCVA in Log MAR scale in group A, group B, group C were comparable.

In the present study average number of injections required for the completion of 12 months follow-up after last injection in group A, group B, group C were respectively 7±1.68, 6.35±1.13, 5.28±1.34. A study by Lai K et al., in the population of mainland China showed that a 1+PRN protocol over 12 months required 6.83 injections on average [10]. Gedar Totuk OM et al., conducted a study in which they have seen a requirement of 6.1 injections were needed over 24 months [11]. Prunte C et al., in their "RETAIN study" showed the mean number of injections was 12.4 and 12.8 in the T&E + laser and T&E groups and 10.7 in the PRN group [8]. A study by Ziemssen F et al., in Germany needed 4.42 injections over first year under T&E protocol [12].

In the present study, after patients receiving treatment with IVR in various protocols over nine months had shown significant reduction of CMT irrespective of the protocol type. On subsequent follow-up at six months and one year since end of therapy had shown varied picture. In monthly protocol and T&E protocol there was no significant change in CMT from the end of the treatment keeping adequate HbA1c control (HbA1c<7.4) over next one year. While patients receiving IVR under PRN guideline had experienced significant bounce back of CMT after stoppage of treatment at one yearly follow-up (p=0.0487 at one year follow-up). In all the cases, HbA1c level was adequately controlled. Lai K et al., in their study showed decreased CMT from 478.23±172.31 µm at baseline to 349.74±82.21 µm, 313.52±69.62 µm, 292.59±61.07 µm, 284.67±69.85 µm, 268.33±43.03 µm, and 270.39±49.27 µm at time point of 1, 2, 3, 6, 9, and 12 months respectively (p<0.05) [10]. The study by Gedar Totuk OM et al., observed significant improvements in CMT at six months (p=0.036), at 12 months (p=0.013), at 18 months (p=0.021), and 24 months (p=0.021) in non vitrectomised eyes, respectively [11]. Prünte C et al., found similar results in both one year and second year follow-up [8].

In this study, all three groups experienced significant improvement of BCVA at end of treatment from baseline (p<0.001). On six month and one year follow-up after end of treatment group A and group C show the best results without any significant deterioration of BCVA from final achieved value. In group B at 12 monthly follow-up following commencement of treatment, worsening of BCVA was statistically significant. Although the net effect of betterment of BCVA from baseline have been maintained even after one year of stoppage of therapy irrespective of the protocol keeping adequate

HbA1c control (HbA1c <7.4). Ziemssen F et al., described that mean baseline VA was 60.6 (95% CI: 59.7; 61.5) early treatment DR study letters. VA improved by C 15 letters in 21.5% and 23.5% of the participants at 12 months and 24 months, respectively. It was concluded that despite fewer injections given compared to randomised controlled trials, with a consequently reduced overall mean visual gain, a profound functional improvement (C 15 letters) was achieved over two years in 23.5% of eyes with DME [12]. Prünte C et al., observed T&E regimens were non inferior to PRN based on mean average BCVA change from baseline to 1-12 months (T&E + laser: +5.9 and T&E: +6.1 vs PRN: +6.2 letters; both p<0.0001). Mean BCVA change at 24 months was similar across groups (+8.3, +6.5 and +8.1 letters, respectively. The T&E regimens showed 46% reduction in the number of clinic visits. Over 70% of patients maintained their BCVA, with treatment intervals of ≥2 months over 24 months [8]. Gedar Totuk OM et al., revealed mean BCVA improved significantly during the 24 month period [11]. Lai K et al., in their study have published that logarithm of minimal angle of resolution (LogMAR) BCVA improved from 0.64±0.23 at baseline to 0.56±0.27, 0.53±0.26, 0.47±0.25, 0.44±0.32, 0.47±0.26 and 0.46±0.26 at 1, 2, 3, 6, 9, and 12 months respectively (p<0.05 for any follow-up time point except first month). It was concluded that older age, lower baseline BCVA, VMT, and disruption of ellipsoid zone are predictors for final poor BCVA while Posterior Vitreous Detachment (PVD) is a positive predictive factor for good final BCVA [10].

Limitation(s)

The main limitation of this study is the smaller sample size. A larger study sample in each group would have provided a more holistic view on the scenario. Other than that, a longer study with further follow-up would provide better results.

CONCLUSION(S)

In this detailed study, there has been focus on the practical scenario as long-term effect of IVR given under different protocols keeping adequate HbA1c control (HbA1c <7.4). In this study, the results were evident that in spite of requiring maximum numbers of injections in PRN protocol, the long-term efficacy was inferior among all. The results clearly indicate that the T&E protocol is as good as monthly protocol and both are superior to PRN protocol when all the protocols were continued for nine months for maintaining long-term benefit. But keeping in mind the socio-economic scenario in our population the burden of regular monthly affordability of injection Ranibizumab is quite difficult and here comes the importance of T&E protocol protocols. Comparing the cost burden for requirement of injections, T&E protocol require significantly least amount of injections for maintaining apparently acceptable long-term treatment outcome comparing from baseline only by keeping adequate HbA1c control (HbA1c <7.4). Hence, it was concluded that T&E protocol of IVR given over nine months may be a good choice for treatment of NPDR with DME in India.

REFERENCES

[1] Romero-Aroca P, Baget-Bernaldiz M, Pareja-Rios A, Lopez-Galvez M, Navarro-Gil R, Verges R. Diabetic macular edema pathophysiology: Vasogenic versus inflammatory. J Diabetes Res. 2016;2016:2156273. Doi: 10.1155/2016/2156273. Epub 2016 Sep 28.

[2] Brownlee M. The pathobiology of diabetic complications: A unifying mechanism. Diabetes. 2005;54(6):1615-25. Doi: 10.2337/diabetes.54.6.1615.

[3] Lucentis (ranibizumab). FDA Approval History- Drugs.com. (n.d.). Retrieved June 23, 2020. Available from: https://www.drugs.com/history/lucentis.html.

[4] Aderman CM, Garg SJ. Intravitreal Anti-VEGF Injection Treatment Algorithms for DME. Retina Today. 2017:53-55.

[5] Chou TH, Wu PC, Kuo JZ, Lai CH, Kuo CN. Relationship of diabetic macular oedema with glycosylated haemoglobin. Eye (Lond). 2009;23(6):1360-63. Doi: 10.1038/eye.2008.279. Epub 2008 Sep 12.

[6] Ferris FL, Kassoff A, Bresnick GH, Bailey L. New visual acuity charts for clinical research. American Journal of Ophthalmology. 1982:94(1):91-96.

[7] Schulze-Bonsel K, Feltgen N, Burau H, Hansen L, Bach M. Visual acuities "hand motion" and "counting fingers" can be quantified with the freiburg visual acuity test. Investigative Ophthalmology and Visual Science. 2006;47(3):1236-40.

[8] Prünte C, Fajnkuchen F, Mahmood S, Ricci F, Hatz K, Studnička J, et al; RETAIN Study Group. Ranibizumab 0.5 mg treat-and-extend regimen for diabetic macular oedema: the RETAIN study. Br J Ophthalmol. 2016;100(6):787-95. Doi: 10.1136/bjophthalmol-2015-307249. Epub 2015 Oct 9.

[9] Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, et al. RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012;119(4):789-801. Doi: 10.1016/j.ophtha.2011.12.039.

[10] Lai K, Huang C, Li L, Gong Y, Xu F, Zhong X, et al. Anatomical and functional responses in eyes with diabetic macular edema treated with "1 + PRN" ranibizumab: One-year outcomes in population of mainland China. BMC Ophthalmol. 2020;20:229.

[11] Gedar Totuk OM, Kanra AY, Bromand MN, Kilic Tezanlayan G, Ari Yaylalı S, Turkmen I, et al. Effectiveness of intravitreal ranibizumab in nonvitrectomised and vitrectomised eyes with diabetic macular edema: a two-year retrospective analysis. J Ophthalmol. 2020;2020:2561251. Doi: 10.1155/2020/2561251.

[12] Ziemssen F, Wachtlin J, Kuehlewein L, Gamulescu MA, Bertelmann T, Feucht N, et al; OCEAN study group. Intravitreal Ranibizumab Therapy for Diabetic Macular Edema in Routine Practice: Two-Year Real-life data from a non interventional, multicenter study in Germany. Diabetes Ther. 2018;9(6):2271-89. Doi: 10.1007/s13300-018-0513-2. Epub 2018 Oct 4.

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