COMPARISON OF TWO INTRAVITREAL RANIBIZUMAB TREATMENT SCHEDULES FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

Bhaskar Gupta, Temilade Adewoyin, Sheryl Patel, Sobha Sivaprasad

COMPARISON OF TWO INTRAVITREAL RANIBIZUMAB TREATMENT SCHEDULES FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

Bhaskar Gupta

Temilade Adewoyin

Sheryl-Kay Patel

Sobha Sivaprasad

AFFILIATION
King's College Hospital
Denmark Hill, London, UK.

CORRESPONDENCE TO:

Ms. Sobha Sivaprasad DM, MS, FRCOphth
Consultant Ophthalmologist
King's College Hospital
Denmark Hill
London, SE5 9RS
Ph No: 02032994548
Fax: 02032993738
Sobha.sivaprasad@nhs.net

Key Words
Ranibizumab

Neovascular age-related macular degeneration.

Word Count: 1910

ABSTRACT

Introduction

Ranibizumab (Lucentis), a humanized antibody fragment that inhibits vascular endothelial growth factor (VEGF-A), is widely used for the treatment of neovascular age-related macular degeneration (NV-AMD). The objective of this study was to compare the outcomes of two different treatment protocols: loading dose (LD) and a *pro re nata* (PRN) dosing schedule from baseline.

Methods

This retrospective chart review was conducted at King's College Hospital, London, UK. Consecutive patients were identified using the "Ranibizumab in NV-AMD" database. These patients had treatment-naive choroidal neovascularization (CNV) secondary to AMD, received ranibizumab therapy and had completed 12 months of follow-up. Baseline examination included visual acuity (ETDRS letters), slit-lamp biomicroscopy, fluorescein angiography, and qualitative and quantitative assessment of central macular characteristics on optical coherent tomography (OCT). Intravitreal ranibizumab (0.5 mg/0.05 ml) was given to all patients at baseline. Patients on LD regimen received two further consecutive monthly intravitreal ranibizumab injections independent of clinical findings. Further injections were determined by the same re-treatment criteria as patients on PRN schedule from baseline.

The main outcome variables in the two treatment groups were visual acuity and central macular thickness at different time points.

Results

The LD group contained 47 patients and the PRN group contained 31 patients. There were no significant differences between groups in the mean changes in visual acuity or central macular thickness. Visual acuity was similar in both groups at 6

months. However, twice as many patients improved visual acuity by 15 or more letters in the LD group (29.8% in the LD group compared to 12.9% in the PRN group [p=0.01]).

Conclusion

This study showed that standard protocols used for OCT-guided retreatment achieved smaller mean gains in vision than those obtained with monthly ranibizumab administration. Further, loading doses of ranibizumab resulted in more visual gains than the PRN protocol.

INTRODUCTION

Ranibizumab (Lucentis) is a humanized antibody fragment designed to bind and inhibit all vascular endothelial growth factor (VEGF-A) isoforms.[1] It is currently indicated for use in neovascular age-related macular degeneration (NV-AMD) based on the MARINA and ANCHOR trials, which showed that monthly intravitreal injections of the drug stabilized visual acuity in 90-95% of patients irrespective of lesion subtype and improved visual acuity in 1 in 3 cases[2;3]. In 2006, the United States Food and Drug Administration approved the use of ranibizumab for the treatment of NV-AMD. Following analyses of clinical efficacy and cost-effectiveness of the drug for this condition, the National Institute of Clinical Excellence (NICE) in the UK approved the use of this drug as a loading dose (LD) consisting of three initial injections at monthly intervals followed by OCT (optical coherence tomography) guided re-treatment[4]. Many patients were initiated on this therapy as soon as the drug was licensed and before the NICE appraisal was completed. These patients received a pro re nata (PRN dosing schedule) based on an OCT-guided re-treatment criteria from the start of the therapy. The objective of this study is to compare the outcomes of the two different protocols: Loading dose (LD) versus PRN dosing schedule from baseline (LD versus PRN).

Methods

This retrospective chart-review was conducted at King's College Hospital. The Institutional Review board and the Clinical Effectiveness Department of the hospital approved the project. The PRN cohort was defined as the cohort before the implementation of the NICE guidance and the LD cohort included consecutive patients soon after the changes of treatment regimen was made to comply with the guidance. All patients were treatment–naive NV-AMD that were initiated on

ranibizumab therapy and have completed at least 12 months follow-up. Eyes with subfoveal choroidal neovascularisation (CNV) secondary to AMD of any lesion subtype with lesion size of less than 12 disc areas and visual acuity between 24 and 73 ETDRS (Early Treatment Diabetic Retinopathy Study) letters were included. Exclusion criteria included patients with CNV secondary to causes other than AMD, lesions previously treated with laser photocoagulation, intravitreal triamcinolone, intravitreal bevacizumab or photodynamic therapy.

Baseline examination

Each patient underwent best corrected visual acuity measurement with ETDRS charts at 2 metres and slit-lamp biomicroscopy. Fundus fluorescein angiography was done to assess the lesion characteristics. Baseline qualitative and quantitative assessment of central macular characteristics were measured by OCT (Stratus III OCT, Carl Zeiss, Dublin, CA) utilizing 6 diagonal 6-mm radial line scans and fast macular thickness scans respectively. Intravitreal ranibizumab (0.5mg/0.05ml) was given to all patients at baseline.

Re-treatment criteria

Follow-up assessments of visual acuity were done by trained personnel in a busy clinic setting and refraction was not repeated. Biomicroscopy and OCT examinations were done at each monthly visit. Fundus fluorescein angiography was repeated only if an increase in lesions size or new haemorrhage was noted on slit lamp biomicroscopy. Patients on LD regimen received two further consecutive monthly intravitreal ranibizumab injections independent of clinical findings. Further injections were determined by the same re-treatment criteria as patients on PRN schedule from baseline.

Criteria for retreatment included persistence 1) recurrence of any subretinal fluid or intra-retinal fluid on OCT in a previously dry macula; 2) increase or new sub-retinal fluid (SRF) and/or intraretinal fluid (IRF) on OCT; 3) decrease of five letters in visual acuity associated with fluid on OCT; 4) new subretinal or intraretinal haemorrhage and/or angiographic evidence of increase in lesion size.

The presence of pigment epithelial detachments (PED) was not considered as a re-treatment criterion.

Outcome measures

Main outcome variables in the two treatment groups were visual acuity and central macular thickness at different time points. One month was defined as an interval of 30±10 days. Last observation carried forward method was applied to replace missing values to the last measurement. The influence of baseline lesion characteristics on final visual outcome was analyzed using a linear regression model. Statistical significance was set at $p<0.05$ for all analyses.

Results

Patient Demographics

Seventy-eight eyes of 78 consecutive patients that met the inclusion criteria were included in this study. There were more females (n=50) than males (n=28). Average age of patients was 80.67 years (range 67-91). Mean duration of symptoms was 3.28 months (range 1 week -12 month). Average time interval from point of first diagnosis (optician or general ophthalmologist) to treatment was 5.3 weeks (range 0-24). The main reasons for the delay to initiate treatment were delay in referral from one hospital to another and approval of funding of the drug before the recommendations of NICE guidelines in 2008. The baseline characteristics of the two groups are shown in Table 1.

Table 1. Baseline characteristics of the patients in the two groups.

	LD regimen	**PRN regimen**	**p-value**
Sex	31 Female: 16 Male	19 Female: 12 Male	0.65
Age (years)	81.39 ± 5.91 (range:67 - 91)	81.90 ± 5.99 (range: 75 - 90)	0.38
Onset of symptoms (in months before diagnosis)	3.48 months (range: 2 weeks - 12 months)	2.93 months (range: 1week - 4 months)	0.13
Interval between diagnosis and treatment (weeks)	5.93 (range: 0 - 24)	4.48 (range 0 - 17)	0.78
Subtypes of CNV	Classic/Predominantly Classic: 27.66%	Classic/Predominantly Classic: 16.13%	0.67
	Minimally Classic: 21.28%	Minimally Classic: 32.26%	0.57
	Occult: 51.06%	Occult: 51.61%	0.15

Notes: LD = Loading dose; PRN = *pro re nata*; CNV = choroidal neovascularization.

Visual outcome

Baseline mean visual acuity at baseline was 48 ± 15.25 ETDRS letters in the LD group and 44.48 ±15.41 ETDRS letters in the PRN group. The proportions of patients that gained vision (≥15 letters) was 29.8% in the LD group compared to 12.9% in the PRN group (p=0.01). There were no statistical differences in the proportions that stabilized vision (loss of less than 15 letters) or lost vision (loss of 15 or more letters) in the two groups at 12 months (table 2). There were also no significant differences in mean change in visual acuity at any time-point during the 12 months (figure 1). At the end of 12 months, the LD group gained a mean of 4.44

letters from while the PRN group gained 4.03 letters. The maximum mean gain in visual acuity was noted at the end of 3 months in LD of +7.7 letters while the PRN group reached a maximum of + 6.2 letters at 6 months.

Table 2. Visual outcome (ETDRS letters) in the two groups.

	LD regimen (n = 47 eyes)	**PRN regimen (n = 31 eyes)**
Mean baseline visual acuity	48 ± 15.25	44.48 ±15.41
Mean visual acuity at 3 months	53.55 ± 18.08 11/47(23.40%) ≥ 15 letter gain 46/47 (97.87%) stable 1/47 (2.12%) ≥ 15 letter loss	51.83 ± 18.08 7/31(22.58%) ≥ 15 letter gain 31/31 (100.00%) stable 0/31 (0.00%) ≥ 15 letter loss
Mean visual acuity at 6 months	55.46 ± 18.68 12/47 (25.53%) ≥ 15 letter gain 45/47 (95.74%) stable 2/47 (4.25%) ≥ 15 letter loss	49.64 ± 18.69 7/31 (22.58%) ≥ 15 letter gain 29/31 (93.54%) stable 2/31 (6.45%) ≥ 15 letter loss
Mean visual acuity at 9 months	51.29 ± 19.61 12/47 (25.53%) ≥ 15 letter gain 43/47 (91.49%) stable 4/47 (8.51%) ≥ 15 letter loss	49.74 ± 19.72 6/31 (19.35%) ≥ 15 letter gain 29/31 (93.54%) stable 2/31 (6.45%) ≥ 15 letter loss
Mean visual acuity at 12 months	52.44 ± 20.29 14/47 (29.79%) ≥ 15 letter gain 42/47 (89.36%) stable 5/47 (10.63 %) ≥ 15 letter loss	48.51 ± 20.38 4/31 (12.90%) ≥ 15 letter gain 29/31 (93.54%) stable 2/31 (6.45%) ≥ 15 letter loss

Notes: ETDRS = early treatment diabetic retinopathy study; LD = Loading dose; PRN = *pro re nata*.

Central Macular Thickness (CMT)

There was no significant differences in CMT at any time points (table 3).The influence of baseline lesion characteristics (SRF, IRF, PED, macular volume) on the initial visual acuity and final visual acuity post treatment was analysed using a stepwise linear regression model with SRF, IRF and PED handled as categorical variables (table 4). None of the baseline characteristics were found to have any influence on outcome post treatment between the two groups.

Table 3. Comparison of change in central macular thickness in the two treatment groups over time.

Treatment Group	1 mth	2 mth	3 mth	6 mth	9 mth	12 mth
LD	-48.5	-73.0	-56.0	-44.0	-33.0	-37.5
PRN	-51.0	-28.0	-20.0	-31.5	-33.5	-43.5
P value	0.61	0.08	0.06	0.74	0.81	0.62

Notes: LD = loading dose of 3 injections; PRN = *pro re nata*

Table 4. Regression analysis investigating the influence of baseline lesion characteristics on final visual outcome.

Variables	***Coefficient***	***Standard Error***	***P value***	***95% Lower***	***95% Upper***
Sex	6.825	3.578	0.0609	-0.321	13.970
Age (years)	-0.106	0.238	0.6576	-0.580	0.369
Laterality	-0.656	3.711	0.8602	-8.067	6.755
Symptom duration (months)	-1.335	0.900	0.1429	-3.134	0.463
Lesion type	-1.136	1.676	0.5006	-4.484	2.212
Baseline visual acuity	0.953	0.135	0.2000	0.683	1.223
OCT central thickness	0.0461	0.0348	0.1903	-0.0235	0.1156
OCT central volume	1.756	1.992	0.3814	-2.223	5.734
SRF	-13.692	6.887	0.0510	-27.446	0.063
IRF	0.757	3.785	0.8422	-6.803	8.317
PED	3.367	3.626	0.3565	-3.874	10.609
Lesion size (disc area)	-6.006	3.961	0.1343	-13.917	1.904
Lens status: Phakia/ IOL	0.515	5.740	0.9288	-10.948	11.978

Notes: OCT = optical coherence tomography; SRF = subretinal fluid; IRF = intraretinal fluid; PED = pigment epithelial detachment; IOL = intra-ocular lens.

Treatment frequency

The mean number of ranibizumab injections was 4.5 in the PRN group and 6.00 in the LD group. Overall 422 injections were performed for this cohort during the 12 month period, with a mean number of injections of 5.41. The distribution of injections every 3 months in the two groups is shown in table 5. The mean numbers of injections received by the two groups at different time points are shown in figure 2. At the time of last follow up, 15/47 (31.91%) eyes in LD group and 11/31 (35.48%) in the PRN group were still active as defined by the criteria for re-treatment stated above.

Table 5. Relation of injection frequency with each regiment.

	0 - 3 months	**4 - 6 months**	**7 - 9 months**	**10 - 12 months**	**Total Injection**
LD (n = 47)	141 (mean 3)	46 (mean 0.87)	50 (mean 1.06)	49 (mean 1.04)	286 (mean 6)
PRN (n = 31)	53 (mean 1.77)	32 (mean 1.03)	23 (mean 0.78)	30 (mean 0.97)	136 (mean 4.5)
Total	194	77	72	79	422
p-value	P = 0.63	P = 0.66	P = 0.64	P = 0.65	P=0.61

Mean number of injections: 5.41 for the whole cohort.
Note: LD = loading dose; PRN = *pro re nata.*

Sub-group analyses

The patients in the PRN group were classified into those that required less than or equal to 3 injections or more than 3 to assess predictive factors that could determine lesions that require less number of injections (Table 6). There were no significant differences in baseline features that could predict the need for less number of

injections. In the PRN group: 9.68% patients received only 1 injection, 64.52% received 2 injections and 25.80% received 3 injections in the first 3 months. Re-analysis of the visual outcome after excluding the patients who received 3 injections in the PRN cohort did not reveal and significant difference. In the LD group, only 12.77% of the eyes received a total of 3 injections only.

Table 6. Sub-group analysis comparing those in the PRN group who required ≤ 3 injections and > 3 injections.

Characteristics	**≤ 3 Injections**	**> 3 Injections**
N (%)	11 (35.4%)	20 (64.6%)
Age in years: mean ± SD	80.27 ± 4.77	82.18 ± 6.16
Range	77 – 91	74 - 97
Male	4	8
Female	7	12
Predominantly classic CNV	2	6
Minimally classic CNV	4	6
Occult CNV	5	8
Mean lesion size ± SD (in DA)	2.47 ± 1.41	2.88 ± 2.48
Range	0.87 - 5.78	0.79 - 11.79
≤ 4 DA: n (%)	9/11 (81.8%)	18/20 (90.0%)
>4 DA: n (%)	2/11 (18.2%)	2/20 (10.0%)
Mean Baseline VA	42.4 ± 13.3	46.0 ± 15.6
Mean VA at 3 month	49.7 ± 18.2	54.35 ± 17.7
Mean VA at 6 month	47.8 ± 19.6	52.4 ± 18.3
Mean VA at 9 month	46.2 ± 19.9	53.7 ± 19.5
Mean VA at 12 month	43.2 ± 23.8	53.1 ± 20.0
OCT CMT		

Proportion with SRF	11/11(100.0%)	18/20(90.0%)
Proportion with IRF	5/11(45.5%)	8/20(40.0%)
Proportion with SRF and IRF	5/11(45.5%)	7/20(35.0%)
Proportion with PED	5/11(45.5%)	9/20(45.0%)

Notes: PRN = *pro re nata*; N = number; SD = standard deviation; DA = disc area; OCT = optical coherence tomography; CMT = central macular thickness; SRF = subretinal fluid; IRF = intraretinal fluid; PED = pigment epithelial detachment; CNV = choroidal neovascularisation..

Complications

Complication included retinal pigment epithelial tear in 7 eyes (4 in LD group and 3 in PRN group) and one eye in the PRN group developed acute anterior uveitis which was successfully treated with a course of topical steroids and cycloplegic drops. All the eyes with retinal pigment epithelial tear had pigment epithelial detachment at baseline presentation. There were no cases of endophthalmitis or retinal detachment.

Discussion

We compared two treatment regiments with ranibizumab for NV-AMD. The LD received a loading dose of 3 ranibizumab injections followed by an as-needed dosing schedule. The PRN group received ranibizumab injections as-needed from baseline. The re-treatment criteria for the as-needed part of the arms were derived from the PrONTO study that showed that an OCT-guided regiment resulted in a mean gain of +9.3 letters with a mean injection frequency of 5.6[5]. Our study showed that the mean gain in vision in the whole cohort was +4.2 letters with a mean injection frequency of 5.41 injections in 12 months. Although the dosing schedules were different in the two groups, the overall re-treatment criteria after 3 months were similar in the two groups. We also believe that we had a lower threshold to treat compared to the

ProNTO study at 12 months because we did not consider any minimum numerical changes in central macular thickness and treatment was initiated if any fluid was present on OCT. Despite that, the overall result of the cohort showed that the mean gain in visual acuity was only approximately half that obtained in the PrONTO study. Caution should be expressed when we compare our cohort with the PrONTO study because the PrONTO cohort were not treatment-naïve. In fact, the study better reflects the visual gain achieved by the SUSTAIN study of +3.6 letters at 12 months with a mean injection rate of 5.7 at 12 months[6]. The SUSTAIN study evaluated the outcome of 3 loading doses of ranibizumab followed by as-needed OCT-guided dosing regimen on 531 patients with NV-AMD. Similarly, our results also mirror the outcomes of the lucentis monotherapy arm of the MONT BLANC study that showed a mean gain of 4.4 letters with a mean injection rate of 5.1 at end of 12 months. So our study mirrors the results of the SUSTAIN and MONT BLANC studies and demonstrates that a PRN dosing schedule with a mean of 5 injections annually will only result in a gain of approximately one ETDRS line of vision in real-life settings[7].

This study also showed that nearly three times as many patients in the LD group gained vision compared to the PRN group at 12 months. In fact, on further analyses of frequency of injections, the time point of maximum gain of vision in both groups correlates with greatest frequency of injections given. The LD had the maximum mean gain in vision of +7.7 letters at 3 months and these results do not differ significantly with the results obtained in the SUSTAIN study of +5.8 respectively. The PRN group had their maximum visual gain at 6 months (+6.8 letters) and this correlates to the maximum number of injections given to the PRN group in this period. However, the maximum gain in the PRN group is less than the

LD group suggesting that 3 loading doses are required to achieve maximum potential gain of vision.

The visual outcomes at different time points were not dependent on any baseline features of the subfoveal lesion or OCT characteristics. Although the sample size was small for sub-group analyses of the PRN group, there were no obvious predictive factors that determined the groups of patients that required less than 3 injections based on the re-treatment criteria used in this study.

Sub-group analyses of the ANCHOR and MARINA studies indicated that the baseline visual acuity, lesion size and age were the important predictors of final visual outcome. This study did not show any of these factors to be relevant probably due to the smaller sample size but more importantly, it may be due to the fact that the injection frequency may be the most important predictor of final visual outcome. Our study substantiates the study by Dadgostar et al[8] that indicated that visual improvement after ranibizumab is related to the frequency of injections received and not to the resolution of fluid by OCT. Michalova et al[9] demonstrated results similar to the MARINA and ANCHOR study on 185 patients with a mean injection rate of 9 injections in 12 months. Although the baseline mean visual acuity was better (57.6 ±15.5 ETDRS letters) in that study compared to this study, the higher rate of injections may also explain the difference in visual outcome between the studies.

There are two published studies that used a PRN dosing schedule from baseline. Both Rothenbuehler et al[10] and Querques er[11] and associates reported visual acuity comparable to MARINA, ANCHOR and PrONTO studies. Despite the same treatment protocol, the mean number of injections in Rothenuehler study was 5.6 ± 2.9 at 12 months and that of Querques was 5.10 ± 2.5 but our PRN group required a mean of 4.5± 2.0 injections only. The limitations of our study are the

retrospective nature and the lack of standardized visual acuity measurements. However, the mean change in visual acuity in the other eye was -1.5 ETDRS letters suggesting that the report is an accurate estimate of changes in visual acuity. Recent publications of several studies of real-life outcomes of OCT-guided ranibizumab therapy show significant differences in outcomes indicating that re-treatment based on changes in visual acuity and OCT may not be sufficient to obtain optimal results. A recent study showed that other tests of visual function such as microperimetry may be a superior tool compared to visual acuity[12]. Similarly, this study was based on Stratus OCT (Ziess, Germany) and now with the availability of new spectral domain OCT, patients in the same clinic settings are requiring more injections suggesting that we may have under-treated patients previously using time domain OCT.

Despite the significant increase in the number of hospital visits for patients, increased work-load for retinal specialists and consequent increase in economic burden to healthcare providers, this study and the review of published studies show that improvement of visual acuity is best achieved with a loading dose of 3 injections and higher rate of injections. These findings should be validated in further randomised clinical trials.

Disclosure: Sobha Sivaprasad has received research and travel grants from Novartis, Pfizer and Allergan.

Reference List

1. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY et al. Ranibizumab for neovascular age-related macular degeneration. *N.Engl.J Med* 2006;**355**:1419-31.

2. Boyer DS, Antoszyk AN, Awh CC, Bhisitkul RB, Shapiro H, Acharya NR. Subgroup analysis of the MARINA study of ranibizumab in neovascular age-related macular degeneration. *Ophthalmology* 2007;**114**:246-52.

3. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. *Ophthalmology* 2009;**116**:57-65.

4. Fung AE, Lalwani GA, Rosenfeld PJ, Dubovy SR, Michels S, Feuer WJ et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am.J Ophthalmol.* 2007;**143**:566-83.

5. Lalwani GA, Rosenfeld PJ, Fung AE, Dubovy SR, Michels S, Feuer W et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. *Am.J Ophthalmol.* 2009;**148**:43-58.

6. Kirchhof B, Kellner U, Folz F G, and Schlingemann R.O. Visual Acuity and Central Retinal Thickness Response Profiles and Treatment Patterns in Patients With Neovascular AMD Treated With Ranibizumab in the SUSTAIN

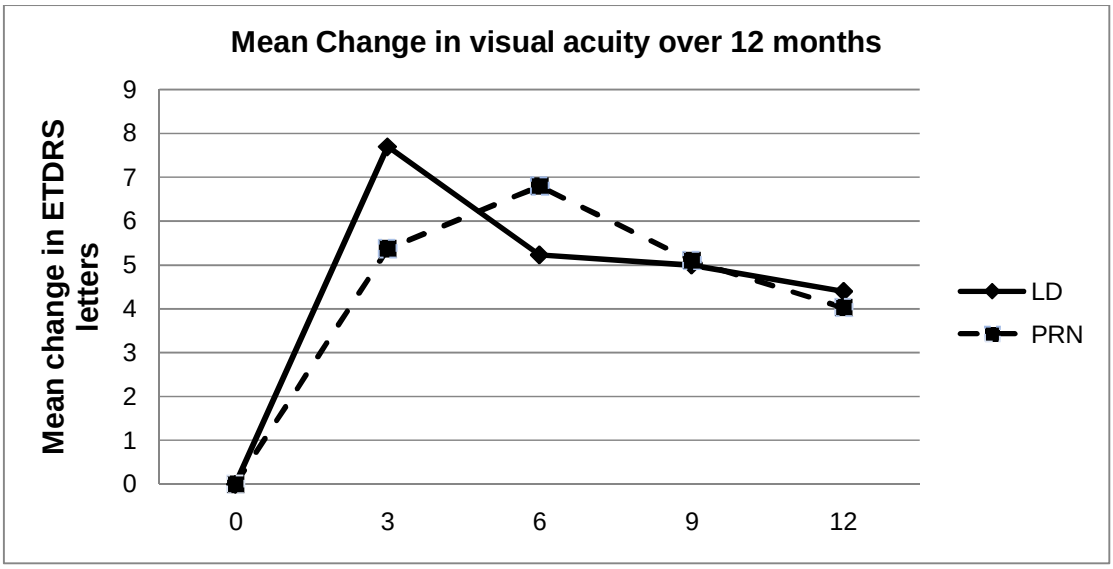
Study**.** On Behalf of SUSTAIN study Group**.** Poster presentation. ARVO 05/05/2009. Ref Type: Conference Proceeding

7. Neuner-Jehle M, Scassellati-Sforzolini B, Dryja T.P, Paulding C, Lewitzky S, He Y, and Farrer L. Clinical Pharmacogenetic Analysis of Patients With Neovascular AMD Treated With Ranibizumab in the EXCITE Trial. Poster Presentation. ARVO . 3-5-2009. Ref Type: Conference Proceeding
8. Dadgostar H, Ventura AA, Chung JY, Sharma S, Kaiser PK. Evaluation of injection frequency and visual acuity outcomes for ranibizumab monotherapy in exudative age-related macular degeneration. *Ophthalmology* 2009;**116**:1740-7.
9. Michalova K, Wickremasinghe SS, Tan TH, Chang A, Harper CA, Downie JA et al. Ranibizumab treatment for neovascular age-related macular degeneration: from randomized trials to clinical practice. *Eye (Lond)* 2009;**23**:1633-40.
10. Rothenbuehler SP, Waeber D, Brinkmann CK, Wolf S, Wolf-Schnurrbusch UE. Effects of ranibizumab in patients with subfoveal choroidal neovascularization attributable to age-related macular degeneration. *Am.J Ophthalmol.* 2009;**147**:831-7.
11. Querques G, Azrya S, Martinelli D, Berboucha E, Feldman A, Pece A et al. Ranibizumab for exudative age-related macular degeneration: 24 months outcomes from a single-center institutional setting. *Br.J Ophthalmol.* 2009.
12. Squirrell DM, Mawer NP, Mody CH, Brand CS. Visual Outcome After intravitreal Ranibizumab For Wet Age-Related Macular Degeneration: A Comparison Between Best-Corrected Visual Acuity and Microperimetry. *Retina* 2009.

FIGURE CAPTIONS

FIGURE 1: Mean change in visual acuity at each follow up visit in the two groups: Loading dose (LD) and pro re nata (PRN).

FIGURE 2: Number of injections in each treatment groups: loading dose (LD) versus pro re nata (PRN) dosing schedule.



Note: LD = loading dose; PRN = pro re nata

Fig.1: Mean change in visual acuity over 12 months in the two groups

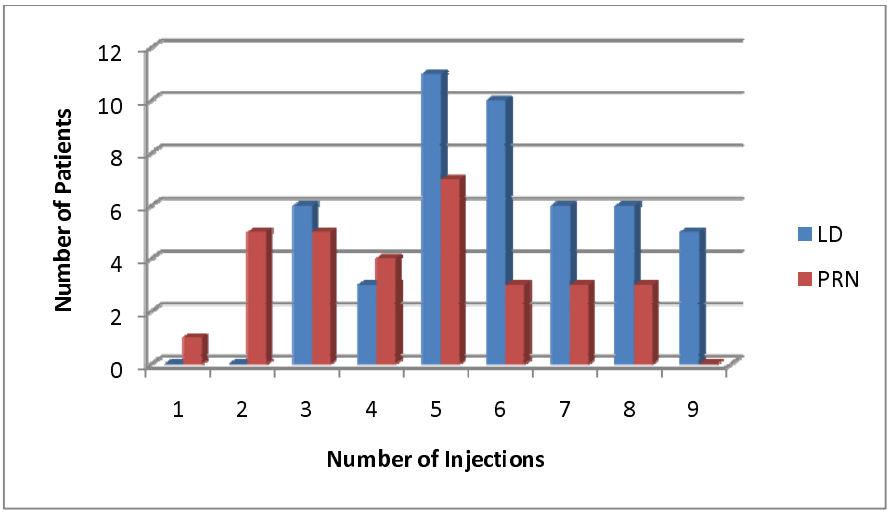


Fig 2: Number of Injections in each treatment group: loading dose (LD) verus *pro-re nata* (PRN) dosing schedule