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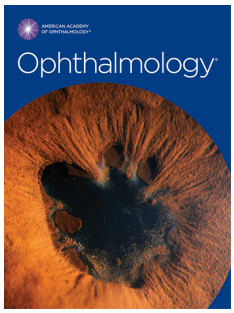

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PII: S0161-6420(20)30556-X

DOI: https://doi.org/10.1016/j.ophtha.2020.06.019

Reference: OPHTHA 11311

To appear in: *Ophthalmology*

Received Date: 23 December 2019

Revised Date: 4 June 2020

Accepted Date: 8 June 2020

Please cite this article as: Spooner KL, Fraser-Bell S, Cozzi M, Staurenghi G, Invernizzi A, Monteduro D, Munk MR, Hong T, Chang AA, Macular Atrophy Incidence and Progression in Eyes with Neovascular Age-Related Macular Degeneration Treated with VEGF Inhibitors Using a Treat-and-Extend or a *Pro-Re-Nata* Regimen. Four Year Results of the MANEX Study., *Ophthalmology* (2020), doi: https://doi.org/10.1016/j.ophtha.2020.06.019.

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Meeting Presentations: Data from this manuscript has been presented at EURETINA annual meeting, Paris, France, September 2019 and Royal Australian and New Zealand College of Ophthalmologists (RANZCO) Annual Congress, Sydney, Australia, November 2019.

Financial Disclosures:
K.Spooner: Has received travel grant from Bayer.
S. Fraser-Bell has acted as consultant for Allergan, Bayer and Novartis.
M.Cozzi: Bayer and Nidek.
G. Staurenghi has acted as a consultant for Novartis, Bayer, Alcon, Allergan, Boeheringer, Genentech, Roche, CenterVue, Heidelberg Engineering, Zeiss Meditech, Optos, Quantel Medical, he has royalties with Ocular Instruments and has received grants from Optovue.
A.Invernizzi has acted as consultant for Bayer and Novartis.
D.Monteduro: none
M.R.Munk: Allergan, Bayer, Novartis, Oculis, Zeiss, Lumithera, Gensight Biologics, Isarna Therapeutics (C)
T.Hong: Has received speaker fees from Allergan and Bayer.
A.Chang, has acted as consultant for Alcon, Allergan, Bayer, Novartis and F. Hoffman-La Roche

Conflict of Interest: No conflicting relationship exists for any author.
Running head: 4-year results of MANEX study. Macular Atrophy Incidence and Progression in nAMD.

ABSTRACT

Purpose: To compare the incidence and progression of macular atrophy (MA) in eyes with neovascular age-related macular degeneration (nAMD) treated with anti-vascular endothelial growth factor (VEGF) agents using either a treat-and-extend (T&E) or a *pro-re-nata* (PRN) regimen over 4-years in a real-life setting.

Design: 4-year, multicenter, retrospective comparative study

Participants: 264 patients with treatment-naïve nAMD.

Methods: Consecutive patients with nAMD received anti-VEGF therapy according to a T&E (n=163) or PRN (n=101) regimen. Eyes were included if they had received anti-VEGF injections for a period of at least 4-years and had annual fundus autofluorescence (FAF) and optical coherence tomography (OCT) imaging using Heidelberg Spectralis. Two masked graders independently delineated areas of MA from serial FAF images using Heidelberg region finder software, and growth rates were calculated. Incident MA was assessed using proportional hazard ratios.

Main Outcomes Measures: MA incidence and progression over 4-years, association between treatment strategy, and number of injections.

Results: At baseline, MA was present in 24% and 20% of study eyes in T&E and PRN groups, respectively (p=0.32). At year-4, 27% (34/124) and 25% (20/81) eyes without baseline MA had detectable MA, in the T&E and PRN groups respectively. In those with MA at baseline, the mean square root area of MA progressed by a rate of 0.4±0.2 and 0.4±0.1mm/year in the T&E and PRN groups, respectively (p=0. 23). Multivariate analysis for baseline predictors of MA growth demonstrated older age, poorer baseline VA and presence of RAP, had a higher risk of greater MA progression (P=0.03). Regression analysis demonstrated no association between T&E and PRN treatment strategies with the risk of developing new MA during the four years of follow-up or the progression of pre-existing MA at year-4 (p=0.692).

Conclusion: Over four years, neither incidence nor progression of macular atrophy in eyes with nAMD treated with anti-VEGF injections was influenced by the treatment regimen and injection frequency. Eyes treated with a T&E regimen received more injections and had better visual outcomes compared to those treated with a PRN approach.

INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is a progressive retinal disease that may cause significant vision loss if untreated [1]. Defects in the retinal pigment epithelium (RPE) layer associated with aberrant choroidal vessel growth cause leak and fluid accrual leading to fast visual decline due to impairment of the overlying retina.[2] Vascular endothelial growth factor (VEGF)-A overexpression is a crucial feature in the pathogenesis of choroidal neovascularisation (CNV).[3,4] Anti-VEGF drugs prevent the binding of several active types of VEGF-A to their receptors and have become the first line treatment for nAMD.[5-8] These agents reduce leak and fluid, and lead to inactivation of choroidal new vessels.

Despite anti-VEGF treatment effectiveness on the neovascular component of the disease, patients with nAMD can develop progressive visual loss due to macular atrophy (MA), a condition characterized by RPE, choriocapillaris and photoreceptors loss.[9,10] Recently there has been some question as to whether RPE atrophy development and progression could be accelerated by more intensive anti-VEGF therapy.[11-13] In fact, VEGF appears to also have an effect on non-vascular tissues and to play a critical role in the survival and maintenance of the RPE and choriocapillaris integrity. Its suppression could therefore induce the development or progression of MA. [14]

The relationship between number of injections and incidence of MA appears to be inconsistent in different studies. The Comparison of AMD Treatment Trials (CATT) found an association between the intensive anti-VEGF therapy and macular atrophy.[15,16] In this study, 18.3% of patients developed MA within 2 years of starting anti-VEGF therapy. At 5-years, eyes on a monthly dosing regimen exhibited a higher risk of developing MA than those on *pro re nata* (PRN) regimen.[16] MA developed in almost all eyes (98%) in the SEVEN-UP study which included eyes treated for nAMD over seven years.[17] In one study, there was an association of MA growth with ocular factors in the study and fellow eyes but not with the number of injections or drug.[18]However, in another study by the same authors, there was an inverse relationship between the number of injections and incidence of MA.[19] A study by Munk et al, demonstrated number of injections were not associated with MA size.[20]

Previous studies have not demonstrated an effect of monthly versus treat and extend dosing on the development of new MA.[21]

Fundus autofluorescence (FAF) is a non-invasive imaging modality used to evaluate the condition of the RPE and the overlying neurosensory retina[22,23], and has become the gold standard by which atrophy is detected and observed.[24] Areas where RPE atrophy is present appear hypoautofluorescent, whereas areas with higher distribution of lipofuscin will appear hyper-autofluorescent.[25] Various limitations have to be considered for FAF imaging. Media opacities may result in FAF images that cannot be analyzed adequately, and FAF changes do not always correlate with RPE changes, such as in cases of soft and hard drusen, haemorrhages and pigmented plaques.[26]However, the FAF images are usually analysed considering and assessing other image modalities such as OCT, to exclude other causes of FAF hypoautofluorescence such as blockage due to hemorrhages or fibrosis.

Our study aimed to examine whether there was a different rate in incidence and/or progression of MA in eyes receiving treatment for nAMD, using a treat and extend (T&E) regimen compared to a PRN regimen. When using a T&E regimen, the aim is to keep eyes free of fluid or 'dry' whereas with PRN approach, eyes are only treated when fluid is present. We hypothesised that there may be a difference in the rate of incidence and progression of MA. In fact, while eyes in the T&E group may develop atrophy at a greater rate due to the more sustained VEGF suppression, greater fluid fluctuations and recurrence of CNV activity may lead to greater RPE injury with resultant atrophy in eyes treated using a PRN regimen.

METHODS

Protocol/Inclusion and Exclusion Criteria and treatment

In this retrospective, multi-center study, consecutive patients undergoing anti-VEGF therapy for neovascular AMD from two retinal clinics in Sydney, Australia and Milan, Italy were included if they fulfilled the following criteria: (1) angiographically confirmed choroidal neovascular membrane (CNV) in the context of nAMD; (2) recurrent and continuous administration of anti-VEGF therapy for the treatment of nAMD to one eye for a minimum of 4-years; (3) the study eye was treatment-naïve at the initiation of treatment; and (4) fundus autofluorescence imaging available at least yearly during the 4 years of follow-up.

Patients who initiated treatment between January 2009 and January 2014, with a minimum follow-up of 4-years were eligible for inclusion. Patients with concurrent intraocular condition that may reduce the potential for visual improvement or impede clinical outcomes, specifically, those with an active diabetic retinopathy, or inflammatory disease such as uveitis, retinal dystrophies, severe media opacities, and RPE rip/tears were excluded.

The study was approved by the local institutional ethics committee (The University of Sydney), and was conducted in accordance with the Declaration of Helsinki.

Data acquisition

Medical records were reviewed for demographic data, visual acuity (VA) converted to an Early Treatment Diabetic Retinopathy Study (ETDRS) letter score,[27] number of intravitreal injections administered, and anti-VEGF therapy administered. The formula to convert Snellen visual acuity measurements to approximate ETDRS letter scores is 85 + 50 × log (Snellen fraction), which may be rounded to the nearest letter.[27] All patients initially received three monthly intravitreal injections, followed by either a PRN or T&E protocol. This study was a retrospective study, and as such strict

criteria for follow-up and retreatment were not pre-established. However, each site followed their own internal guidelines for the management of patients with nAMD. All procedures including follow-up visits took place at the Eye Clinic, Department of Biomedical and Clinical Sciences, Luigi Sacco Hospital, University of Milan and Sydney Retina Clinic, Sydney, Australia. These clinics were chosen as the retinal specialists consistently treated their patients using the one protocol as standard clinical practice already in place in the respective clinics. T&E regimen group consisted of patients from the clinic in Sydney, and PRN group consisted of patients from Milan.

For the first group (PRN), the usual protocol of the treating doctor, was 3 loading doses of anti-VEGF injections, with subsequent injections only given if there was a drop in visual acuity, new haemorrhage or exudation on OCT. After treatment by 3 monthly intravitreal injections of anti-VEGF therapy during the period from January 2008 to January 2014, subsequent single injections were given as needed according to changes in the patient's visual acuity and/or signs of exudation on optical coherence tomography (OCT) or fluorescein angiography (FA). In the absence of retreatment criteria, no further injections were administered, and patients were asked to follow-up again in 4 to 8 weeks.

For the second group (T&E group), the usual protocol of the treating doctor, was 3 monthly loading doses of anti-VEGF treatment. If there was no new haemorrhage or signs of exudation on OCT, the interval between injections was extended a further 2 weeks, up to a maximum of 12 weeks. If new haemorrhage or exudation were present, then the interval was decreased by 2 weeks to a minimum of 4 weeks. The aim of this regimen was to keep the macula dry.

Baseline fundus fluorescein angiographic (FA) and OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) images were graded by 2 independent graders, blinded to site, for active CNV lesion type (type 1, type 2, type 3/retinal angiomatous proliferation (RAP) or polypoidal choroidal

vasculopathy (PCV),[28] and for the presence of atrophy. Fundus autofluorescence imaging (FAF) were obtained on Heidelberg Spectralis using a laser with an excitation wavelength of 488nm and barrier filter of 495nm. Macular atrophy was defined as sharp, delineated hypoautofluorescence with corresponding attenuation of the RPE band and loss of overlying ellipsoid zone and external limiting membrane with thinning of the outer nuclear layer, together with enhanced signal transmission into the choroid as evidenced on OCT.

The quantification of macular atrophy using FAF was performed by two graders, blinded to all patient details, using the Heidelberg region finder software (version 2.5.8.0) (**Figure 1**), which is able to semi automatically quantify atrophic areas. Once atrophic areas and constraints had been defined for the baseline image, they could then be copied to the subsequent visit images.[29] The minimal lesion size was defined as an atrophic area measuring 0.02 mm^2, quantified using region finder software.[30]

Various limitations have to be considered for FAF imaging. Media opacities may result in FAF images that cannot be analyzed adequately, and FAF changes do not always correlate with RPE changes, such as in cases of soft and hard drusen, haemorrhages and pigmented plaques.[26]However, the FAF images are usually analysed considering and assessing other image modalities such as OCT, to exclude other causes of FAF hypoautofluorescence such as blockage due to hemorrhages or fibrosis.

Image quality of FAF were analyzed by two graders, in cases of poor FAF image, multimodal imaging was assessed by both graders for unanimity. In cases of hemorrhage, FAF imaging available within 3 months of target visit was used. In cases where there was a difference greater than 20% between measurements obtained by the two observers, arbitration through open adjudication was performed. In the few cases in which agreement was not achieved, a resolution was established by a third expert grader who evaluated the images (SFB). An average of the measurements of the two observers was used for statistical analysis. Areas of peripapillary atrophy were not classified as MA and accordingly were not included in MA measurements. In images that showed two or more

distinct MA areas each measuring 0.02mm^2 or greater, each distinct area was measured and summed to generate the total MA area.

Incident MA was defined as a well-demarcated region or regions of marked hypo-autofluorescence from an absence of the RPE measuring at least 0.02mm^2. The progression of MA was classified as the expansion of pre-existing areas of MA equated to baseline. The variance in the entire area of MA at each annual visit and baseline were determined and the degree of progression was calculated by dividing the change in MA size by the time points.[31,32] As MA progresses at a non-linear rate, MA size was also calculated as a square root transformation[31] of lesion area to reduce the reliance on baseline lesion size for test-retest variability and the growth rates.[33] All MA results are presented as the square root transformation value. MA that was confluent with peripapillary atrophy were excluded.

The measurement of central subfield retinal thickness (CSRT), defined as the distance from the inner retinal surface to Bruch's membrane within the central 1mm of the ETDRS grid.. All measurements were performed using the Heidelberg Eye Explorer software (version 1.9.10.1; Heidelberg Engineering, Heidelberg, Germany). The results from two independent masked graders were compared. If the difference in quantitative results between graders was less than 20%, the individual grader results were averaged. If the difference was ≥20%, a third examiner adjudicated a consensus among graders.

Intra-observer reliability was evaluated by the intraclass correlation, which was calculated from the measurements of the two graders

Expected patient numbers and power calculations

We estimated that there may be a 15% difference in incidence and progression of MA in eyes treated with the T&E regimen compared to PRN. The prevalence of MA at onset of neovascular AMD varies in the literature of between 6% and 40.9%,[16,21,34] so we assumed a baseline prevalence of MA

of 20% in each group. A total of 236 participants would be required to find a difference between the 2 groups with a power of 80% and false positive rate of 5%.

Statistical Analyses

Statistical analysis was performed using SPSS software (version 24.0, SPSS Inc., Chicago, IL, USA). Results were presented as means and standard deviation. Mann-Whitney's nonparametric test was used to compare statistical distributions. Inter-observer agreement was assessed using the interclass correlation coefficient (ICC). The statistically significant difference between the two treatment groups was also proven by a more robust procedure, Welch test.

Univariate and multivariate analyses with logistic regression were used to determine factors associated with atrophy at baseline and proportion of patients with new MA at each annual visit. In respect to macular atrophy, predictive factors of visual acuity, number of injections, CSRT, and atrophy size were assessed with linear regression. The generalised estimating equation (GEE) was used to account for the inclusion of bilateral eyes from the same patient. A sensitivity analysis using mixed model after data imputation following the LOCF method for mean change in VA was consistent with the secondary analysis. A 95% confidence interval with 5% level of significance was adopted; thus, *P* values of <0.05 were considered to be statistically significant. Missing data were imputed using the last observation carried forward method. Treatment exposure and follow-up frequency were only analysed in patients concluding the entire 4-years of the study.

RESULTS

Study patients

Of 2,041 eyes identified with beginning anti-VEGF treatment between 2009 and 2014, 264 eyes met the inclusion and exclusion criteria. All eyes commenced treatment with intravitreal injections of anti-VEGF injections between 2009-2014, 206 eyes were initiated on ranibizumab treatment, 45 on aflibercept, and 13 on bevacizumab. A total of 163 eyes were treated according to a treat-and-extend regimen (T&E), and 101 eyes were treated according to *pro re nata* (PRN) regimen. Follow-up data were available at least annually for 4-years post initiation of anti-VEGF therapy. Bilateral eyes were included in 24 cases. During the 4-year follow-up period, 130 eyes (49%) changed anti-VEGF therapy at least once (62 eyes in the PRN group and 68 eyes from the T&E group).

Baseline characteristics

The groups were well balanced at baseline for visual acuity (P=0.45) and CSRT (P=0.67). The other demographic and ocular parameters of the two treatment groups are presented in **Table 1**.

The PRN group included 66 women and 35 men, aged from 52 to 91 years (mean, 74.3±8.1 years). This group included 61 eyes with type 1 CNV (60%), 17 eyes (17%) with type 2 CNV, 14 eyes (14%) with type 3 or retinal angiomatous proliferation (RAP), and 9 eyes (9%) with polypoidal choroidal vasculopathy lesions (PCV). Initial visual acuity ranged from 20 to 85 letters with a mean of 65.5±14.7 (Snellen equivalent: 20/50) at baseline.

The T&E group included 82 women and 81 men aged 55 to 95 years (mean, 77.8±8.5 years). There were 68 right eyes and 85 left eyes. This group included 95 eyes (58%) with type 1 CNV, 31 eyes (19%) with type 2 CNV, 21 eyes (13%) with Type 3 (RAP) lesion and 16 polypoidal cases (10%). Initial visual acuity ranges from 20 to 90 letters with a mean of 66.9±14.4 (Snellen equivalent: 20/50).

A predetermined sub analysis assessed the incidence, and progression of macular atrophy. The inter-grader reliability was excellent for both (k=0.91).

Pre-existing Macular Atrophy

At baseline, MA was present in 39 eyes (24%) in T&E group and 20 eyes (20%) in the PRN group (p=0.45). Mean baseline MA area was greater in the T&E group than the PRN group (1.1±0.7mm and 0.8±0.4mm in the T&E and PRN groups, respectively using the square root transformation, *P*=0.06). At year 4, mean MA area increased to 2.2±0.9mm in the T&E group, and 1.7±0.6mm in the PRN group (p=0.06) (**Figure 2**), showing continuous growth over the course of the study regardless of the treatment regimen.

Continuous progression of MA was seen in all eyes with MA at baseline based on FAF and OCT images at each annual visit. The MA progression rate over 4 years for eyes with pre-existing MA was 0.4±0.2mm/year in the T&E group, 0.4±0.1mm/year in the PRN group (*P*= 0.23) (**Figure 2**). All eyes demonstrated increased area with MA, with 93% expanding by 1-disc area or more by 4 years follow-up.

The progression rates by CNV type were significantly higher in the eyes with Type 3 lesions (RAP) (p=0.04), in both groups with a progression rate of 0.9±0.8mm/year and 1.0±0.7mm/year in the T&E and PRN groups respectively (*P*=0.62). The progression rate of MA was smallest in those with type 1 CNV: 0.5±0.2mm/year and 0.3±0.1mm/year in the T&E and PRN groups, respectively (*P*=0.45).

Of all the eyes with MA at baseline, 31% was unifocal and in 69% it was multifocal. The proportion of eyes with unifocal and multifocal MA was similar in each group (p=0.09 and 0.08, respectively). There was no difference in the rate of progression of MA in those with unifocal compared to multifocal MA (0.2±0.1mm/year and 0.3±0.2mm/year, respectively [p=0.68]). In those with MA at baseline, it included the fovea in 58% and was extrafoveal in 42%. There was no difference in the

proportion of foveal involving and extrafoveal MA between the 2 groups (p=0.82 and 0.81, respectively). There was no difference in mean progression rate of MA in foveal involving MA compared to extrafoveal MA (0.5±0.2mm/year vs. 0.6±0.2mm/year, p=0.22). As expected foveal centred MA had lower baseline VA (46.7±15.2 letters vs. 68.4±12.9 letters, p<0.001).

The main outcome, the correlation coefficient among treatment regimen and progression of GA in SQRT, was Pearson's r=0.3, P=0.29. As predicted, the correlation was positive for progression expressed in mm/year, r=0.7, P<0.001 (FIGURE 2). On univariate analysis, increasing age (p<0.001), poorer baseline VA (p=0.02), foveal location of MA (p=0.01), and presence of RAP (p=0.04) and presence of intraretinal fluid (p=0.05), were all associated with increased progression of MA.

Multivariate analysis for baseline predictors of MA growth demonstrated older age, poorer baseline VA and presence of RAP, had a higher risk of greater MA progression (P=0.03). Other variables, such as sex, presence of RSD, drusen, CSRT, lens status and treatment group were not significant.

Incidence of New Macular Atrophy

Incident MA developed in 34 eyes (27% of eyes without MA at baseline) and 20 (25%) eyes in the T&E and PRN groups respectively during 4-years of anti-VEGF therapy (*P*=0.70) **(Figure 4)**. The mean size of MA on first presentation was 1.2±0.9mm^2 and 1.1±1.6mm^2 in the T&E and PRN groups, respectively (*P*=0.88). A total of 13 (10%) T&E eyes and 9 (11%) PRN eyes developed atrophy within the first year of initiating anti-VEGF therapy. The incidence in the 2nd, 3rd and 4th years was, 5 eyes (4%), 9 eyes (7%) and 7 eyes (6%) in the T&E group; and 6 eyes (7%), 3 eyes (4%), and 2 eyes (2%) in the PRN group.

Incidence of MA varied across eyes with different CNV types. particularly those with type 3 (RAP) CNV, that demonstrated greater increase in MA size(*P*=0.04). Subset analysis of incidence of MA for

each CNV subtype, found a higher incidence of MA among those with type 1 CNV (51%), followed by RAP lesions (17%), PCV (15%) and type 2 (7%).

Unifocal lesions accounted for 48% of eyes, and multifocal in 52% of eyes. Multifocal MA had a significantly greater progression rate compared to unifocal lesions (0.4±0.2mm/year vs. 0.2±0.1mm/year, p<0.001). Foveal MA was present in 44% of eyes at baseline, and 56% were classified as extrafoveal. Extrafoveal MA demonstrated a greater mean progression rate compared to foveal MA (0.4±0.2mm/year vs. 0.3±0.1mm/year, p=0.05). Again, as predicted foveal centered MA significantly lost vision by year-4 (-12.9±13.1 letters) compared to those eyes with extrafoveal MA who gained 6.3±9.2 letters, at the end of follow-up, p<0.001).

Overall, there was no significant difference in the risk of developing MA between the two treatment groups during the four years of the study, *P* =0.69. Injection frequency in the T&E group did not appear to be associated with MA presence at year-4 (**Figure 5**). There was no meaningful difference in new MA rates by injection frequency.

Time was a significant predictor of development of new MA by year-4, (*P*<0.001), each year there was a 38% higher risk in developing MA. The presence of PED, reticular pseudodrusen, and number of injections were found to be not significant in predicting the development of new MA.

No significant difference was found regarding gender, pseudophakic status or type of anti-VEGF therapy.

The mean progression rate of MA that developed over the course of the study was 0.8±0.6mm/year and 0.8±0.9mm/year in the T&E and PRN groups respectively (*P*=0.89) **(Figure 6)**.

Linear regression analysis demonstrated a positive association between treatment regimen, with a gain in VA at year-4 in the T&E group (*P*=0.006) compared to baseline. Multiple regression analysis

adjusted for VA, age at diagnosis, OCT findings at baseline demonstrated no association between the T&E and PRN treatment strategies with the progression of preexisting MA at year-4 (*P*=0.09). Multivariate analysis indicated that higher baseline CSRT, type of CNV lesion and presence of intraretinal fluid at year 1 was associated with a higher progression rate of atrophy (*P*<0.001, *P*=0.03, and *P*<0.001 respectively). Eyes in the T&E cohort received a significantly higher number of anti-VEGF injections during the follow-up period (29.3±10.8 versus 15.7±8.8, *P*<0.01). Interestingly, number of injections was not statistically significant as a risk factor for MA progression (*P*=0.06).

Vision and CSRT Outcomes

Baseline CSRT was similar between the treatment groups: 410.2±105.5μm versus 416.6±136.5μm in the T&E and PRN groups respectively (*P*=0.67). There was no significant difference for the first 2 years, but by year 3 there was a significant difference (*P*=0.01) among the T&E and PRN groups (**Figure 7**).

VA was evaluated in eyes in the absence versus presence of MA. Eyes with and without MA at baseline had mean VA gains from baseline to Year 1 of 0.3±8.2 and 2.7±10.9 letters in the T&E group, respectively (*P*=0.10); and 0.5±13.8 and 4.4±12.9 letters, respectively in the PRN group (*P*=0.25). However, these gains were lost by Year-4 in eyes with and without MA at baseline: -0.5±13.6 and +0.9±13.9 in the T&E group respectively, (*P*=0.57); and -4.2±17.2 and -2.6±23.7 in the PRN group respectively, (*P*=0.74) (**Figure 8a).** VA was also evaluated at baseline, year -1, -2, -3 and -4 with and without concurrent MA, that is, eyes with detectable atrophy at baseline at each time point (**Figure 8b**).

Reassuringly, 72 eyes (44%) and 40 eyes (40%) from the T&E and PRN groups respectively, never developed MA during the 4-years of observation (*P*=0.65). Those eyes that developed new MA had a greater decline in vision in contrast to those eyes that never developed atrophy, most evident after 4-years of treatment.

DISCUSSION

VEGF inhibitors have revolutionised the outcomes of eyes with nAMD and decreased the rate of blindness amongst those affected. Despite this, the impact of atrophy on nAMD patient's visual function and quality of life is significant and a correlation between anti-VEGF treatment and a higher MA development/progression has been proposed.[12]

Different treatment regimens for nAMD are used in real life settings in order to control the disease and prevent overtreatment, the commonest being T&E and PRN. Both these approaches may have an impact on MA development/progression. In fact, while eyes in the T&E group may develop atrophy at a greater rate due to the more sustained VEGF suppression, greater fluid fluctuations and recurrence of CNV activity may lead to greater RPE injury with consequent atrophy in eyes treated using a PRN regimen.[12,35,36]

In the MANEX study we compared two group of eyes treated with anti-VEGF following a T&E and a PRN regiment respectively and we compared the incidence and progression of MA between these 2 groups. We found that the incidence of MA and the mean square root area of MA increase was similar in the two groups, regardless of the treatment regimen. Eyes treated with T&E however received significantly more injection than those on a PRN regimen and had significantly better visual outcomes at 4 years.

Natural history studies have shown that MA occurs in eyes with nAMD without anti-VEGF treatment, so susceptibility to macular atrophy is part of the disease process. However, growth rate of MA in untreated eyes is between 1.5 and 2.2mm^2/year over 4 years,[37,38] significantly more to results seen in the present study. This suggests a possible increase in the risk to develop new MA following anti-VEGF treatment regardless of the re-injection strategy, and the possible protective effects of CNV lesions.[39] Despite this, VA in eyes treated with anti-VEGF injections is significantly higher than that of untreated eyes thus the benefit deriving from the neovascular component control overcomes the negative effect of new GA development on VA outcomes, justifying the treatment.

Previously reported incidence of MA in eyes treated with anti-VEGF injections is heterogenous in the literature. In the present study, MA was present in 24% of the T&E group, and 20% in the PRN group at baseline, which is similar to the 24% observed in newly diagnosed treatment naïve nAMD eyes in a study by Sikorav et al[28] whom had a similar baseline mean atrophy size (1.2±1.8mm^2). The incidence of new atrophy developed in 11% and 10% in the PRN and T&E groups, respectively at year-1, a percentage comparable to month-12 findings of the RIVAL study,[34] and in a retrospective study by Kuroda et al,[40] in which newly diagnosed eyes were treated with aflibercept for 12-months. At 4 years 27% of eyes in the T&E group and 25% of eyes in the PRN group developed new MA. These figures are comparable to results seen in the HARBOR study (29%)[41] and slightly below the 24-month results seen in the RIVAL study (27% and 32% in the ranibizumab and aflibercept arms, respectively).[34]

The enlargement of atrophic lesions corresponds to loss of increasingly larger areas of the visual field and almost invariably occurs in eyes affected by MA. A higher rate of progression of these areas could mean a faster loss of VA. For this reason, determining whether a different anti-VEGF injections regimen could affect the MA progression is of extreme relevance. In our study, the change in square root area of MA at 4-years was similar between the two arms. We found a MA growth rate similar to that seen at 24-months of the RIVAL study (0.36 and 0.28mm^2/ year in the ranibizumab and aflibercept arms respectively) and less than that that seen in the CATT study (0.7mm^2/year). This suggest absence of correlation between the treatment regimen. The macular atrophy area demonstrated a positive correlation with larger baseline areas progressing faster, as previously reported.[33] The LOESS regression analysis did not differ from the linear regression, after square root transformation, comparable to results seen in a study by Mones et al.[42]

Using adjusted linear regression analysis, we found no relationship between treatment regimen and progression of existing MA and incidence of new MA over 4-years. We found no significant association with the total number of injections with the apparent growth of MA. Although it is

possible that there were not have enough eyes to power this statistical finding. There was a significant difference in injection rates between the 2 groups, yet the number of injections of anti-VEGF or treatment strategy had no association with the incidence and progression of MA. The injection rates seen in the T&E group were similar to both groups in the RIVAL study, where the mean number administered in the first 12 months was 9.7, and 8.9 in the final 12 months,[34] which is higher than that observed in other observational real-world studies. Although the number of injections in the PRN group in the present study, may explain the poorer visual outcomes compared to T&E group.

Although the CATT trial demonstrated that eyes receiving monthly treatment had a higher incidence of atrophy compared to those being treated with PRN, [16] the IVAN and RIVAL studies found no statistical difference in incidence of atrophy among differing anti-VEGF therapies.[34,43]Injections of intravitreal anti-VEGF has been shown to have no association with RPE damage in animal models.[44-46] A possible explanation for the inconsistent results reported in the literature is that MA could depend more on specific features of the single neovascular lesions included in the studies or the underlying MA phenotype rather than to the treatment itself. Furthermore, the subtype of neovascularisation is believed to influence the risk of atrophy progression. It has been proposed that type 3 (retinal angiomatous proliferation- RAP) lesions may confer a greater risk in the development and progression of atrophy, whilst type 1 are associated with a lower risk of MA progression.[39,47] Our study confirmed this association and it is possible that an uneven distribution of type 3 (RAP) lesion in the arms of the above-mentioned trials affected the post-hoc analysis on MA.

This study has several limitations that must be considered when interpreting the findings. Being a retrospective study, our cohort represents only a subgroup of treated patients, that is those with 4-years of follow-up and adequate imaging, thus selection bias cannot be excluded. It is possible that patients were not always compliant with the recommended follow-up. Furthermore, a limitation of the study common to longer term studies was the eyes excluded due to insufficient data or lost to

follow-up of patients. It is possible that patients who responded extremely well or especially poor were more likely to cease treatment or be lost to follow-up, thus limiting generalizability of the findings. This would affect the aggregate data, notwithstanding these limitations, these would not change the main conclusions of the study, which are centred on comprehensive examinations made in each patient over-time. Finally, the Heidelberg Region Finder Software, to the best of our knowledge, is so far, the only validated method to assess atrophy in CNV, however, we are aware it has limitations such as masking due to fibrosis and disease activity.[28,30,34,48-50] These changes sometimes lead to irregular, not clearly demarcated hypoFAF lesions. This can impact the assessment using the region finder.

Our study was not powered to compare difference between anti-VEGF agents. However, previous studies including the RIVAL study and the CATT did not find a difference in the development or incidence of MA in eyes treated with ranibizumab vs aflibercept or ranibizumab vs bevacizumab.[16,34] Finally, a proportion of patients (49%) within our study switched agents during the 4-year follow-up period. However, the large number of patients and long follow-up make this data set an extremely valuable addition to the literature.

In conclusion, the MANEX observational study found no significant difference in the incidence or progression of MA in eyes with nAMD treated with anti-VEGF intravitreal injections using a T&E or PRN regimen over 4-years. Eyes treated using a T&E regimen had significantly better visual outcomes and received more injections. Since visual outcomes are better with a T&E protocol and the present study demonstrated that MA is not influenced by the frequency of treatment, T&E may be the preferred treatment regimen as it allows for better functional outcomes with no increased risk for MA.

Figure Captions

Figure 1: Example of measurement of atrophy area by two masked graders using Heidelberg Region Finder semi-automatic progression tool at (A) baseline; (B) Year 1; (C) Year 2; (D) Year 3; and (E) Year 4.

Figure 2: Mean progression of macular atrophy (MA) area over 4-years of follow-up in eyes with pre-existing atrophy (n=59).

Figure 3: Mean change in macular atrophy (MA) area by square root (SQRT) transformation over 4-years of follow-up in eyes with pre-existing atrophy (n=59).

Figure 4: Incidence of New Atrophy over 4-years

Figure 5: Total number of injections received (n=264).

Figure 6: Mean change in macular atrophy (MA) area over 4-years of follow-up in eyes with new incident atrophy.

Figure 7: Mean change in central macular thickness (CSRT) over 4-years of follow-up.

Figure 8: Visual Acuity (VA) in the presence and absence of detected macular atrophy (MA). **A**, VA change from baseline over time among study eyes with and without MA detected at baseline. **B,** VA at baseline, year 1, year 2, year 3, and year 4 with and without MA detected at each time point. Error bars in both **A** and **B**, 95% confidence intervals (CIs) are shown. ETDRS= Early Treatment Diabetic Retinopathy Study.

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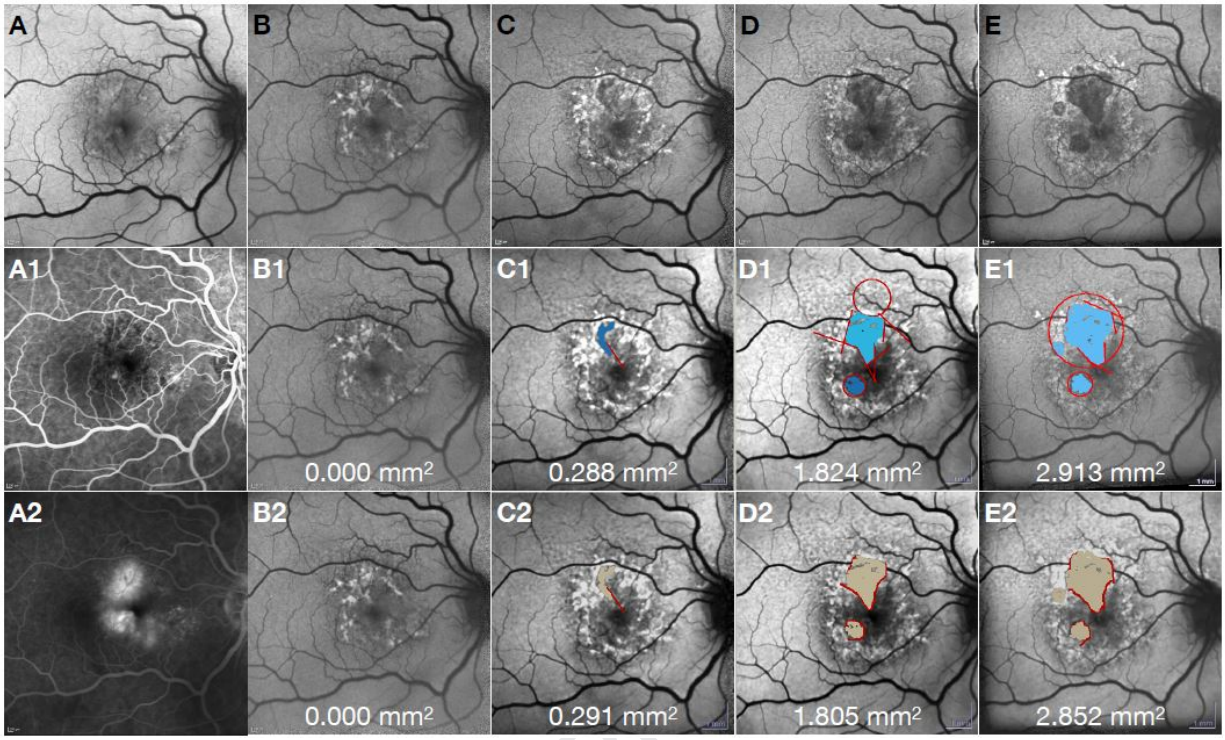
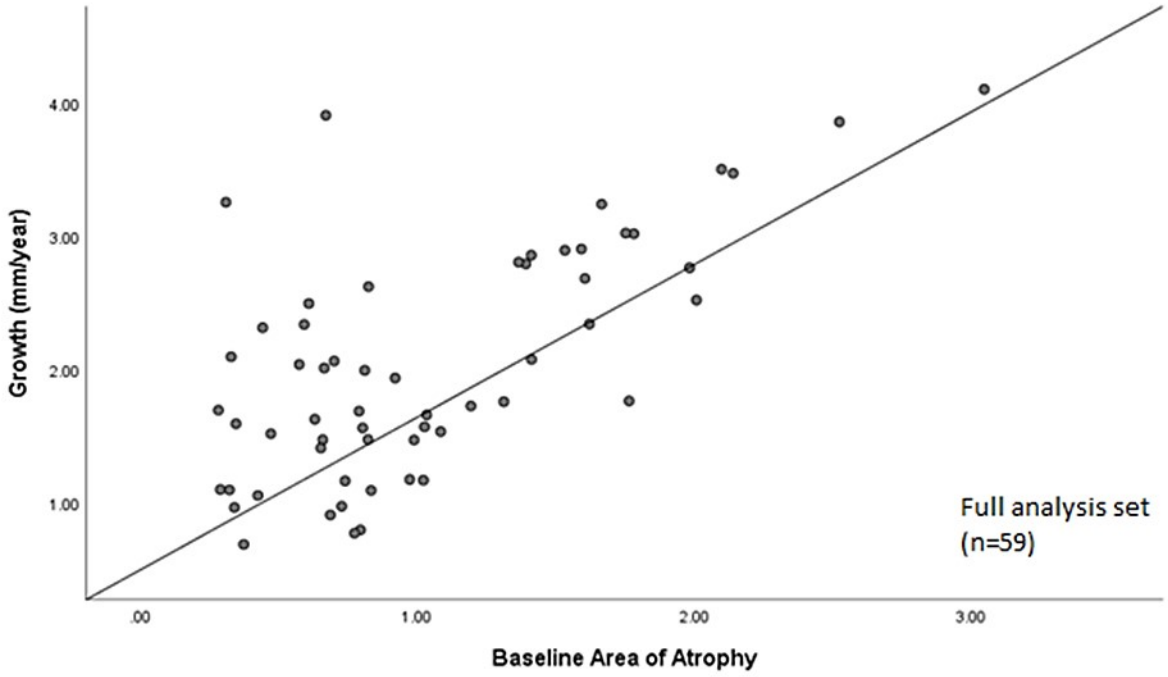
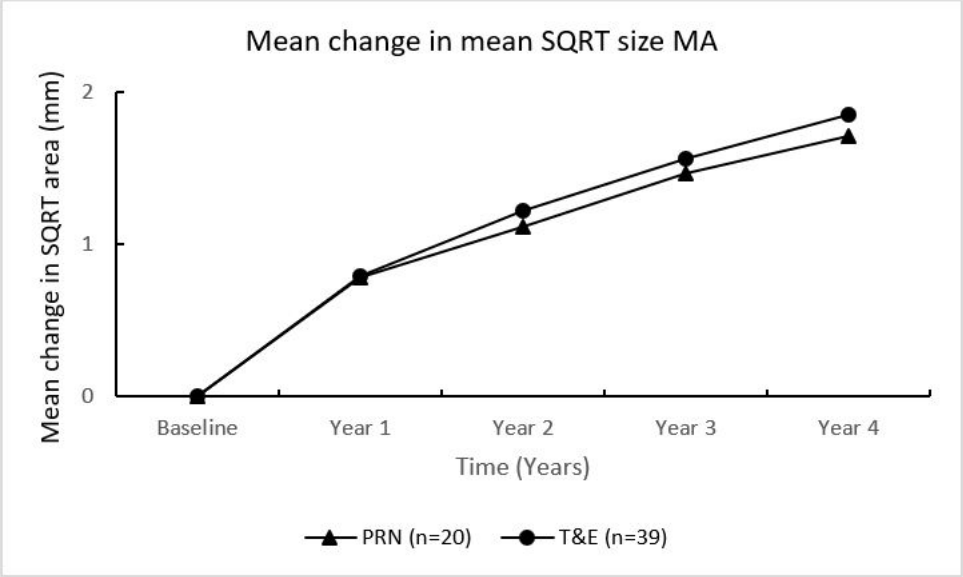
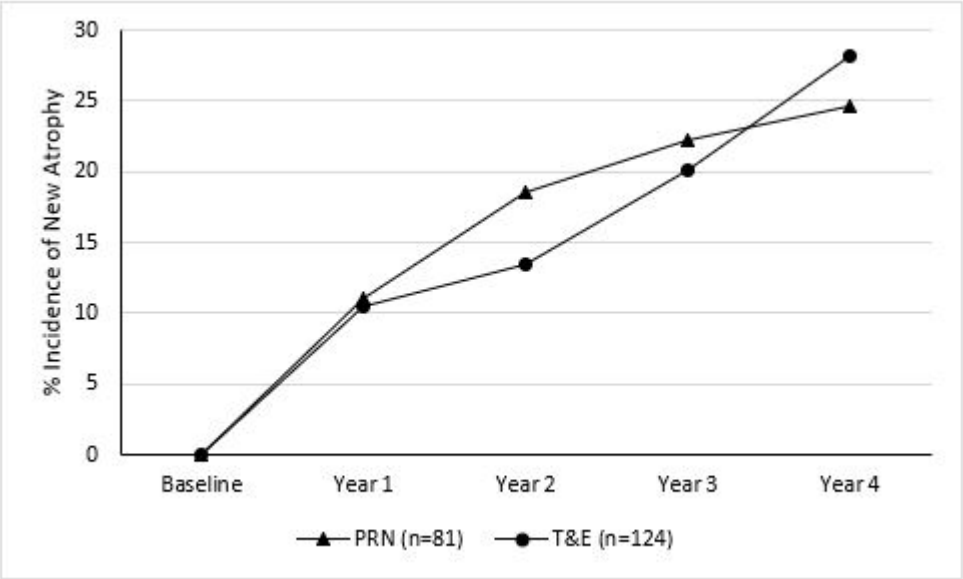
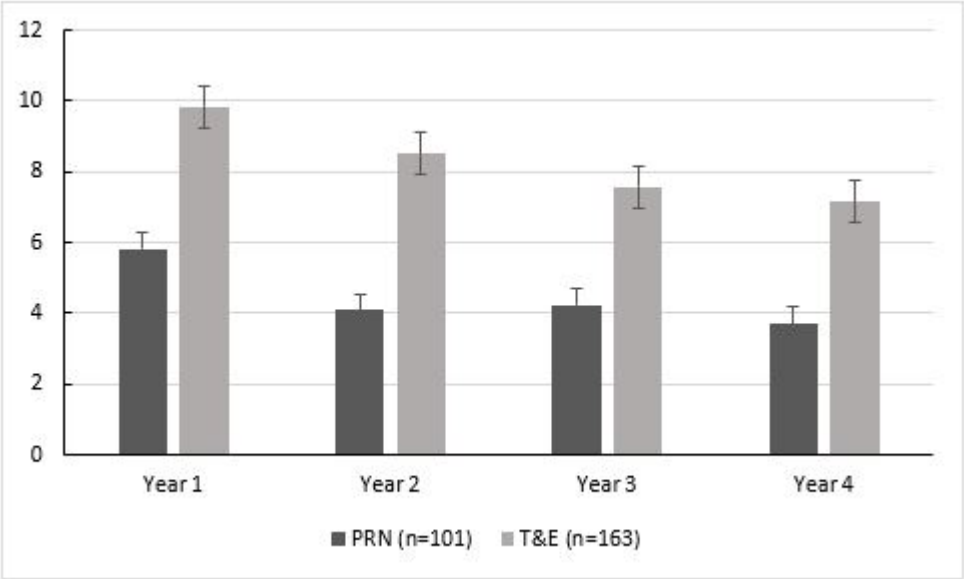
Precis: This comparative study of 264 eyes with nAMD treated with VEGF inhibitors demonstrated no difference in incidence or progression of macular atrophy using a treat-and-extend versus Pro re nata regimen over 4-years.

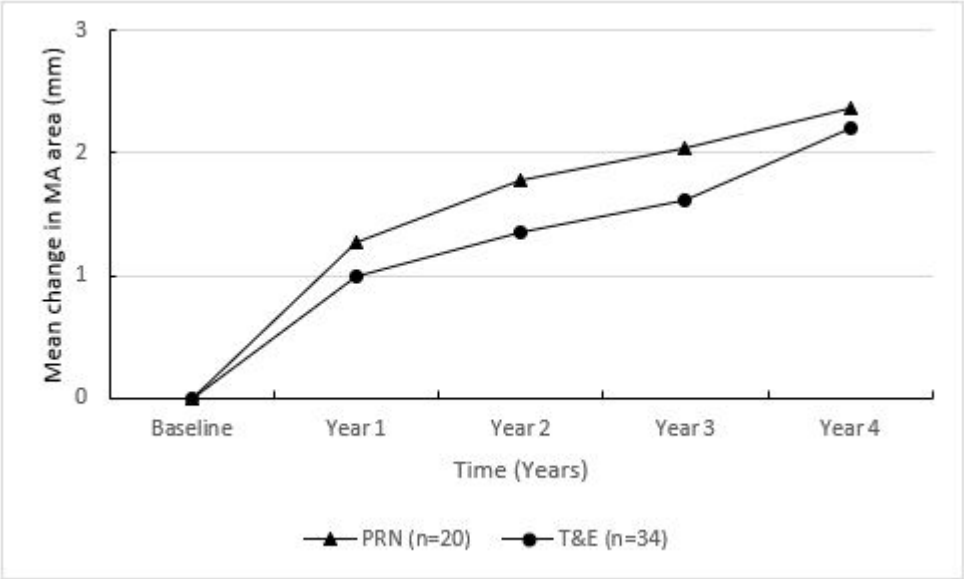


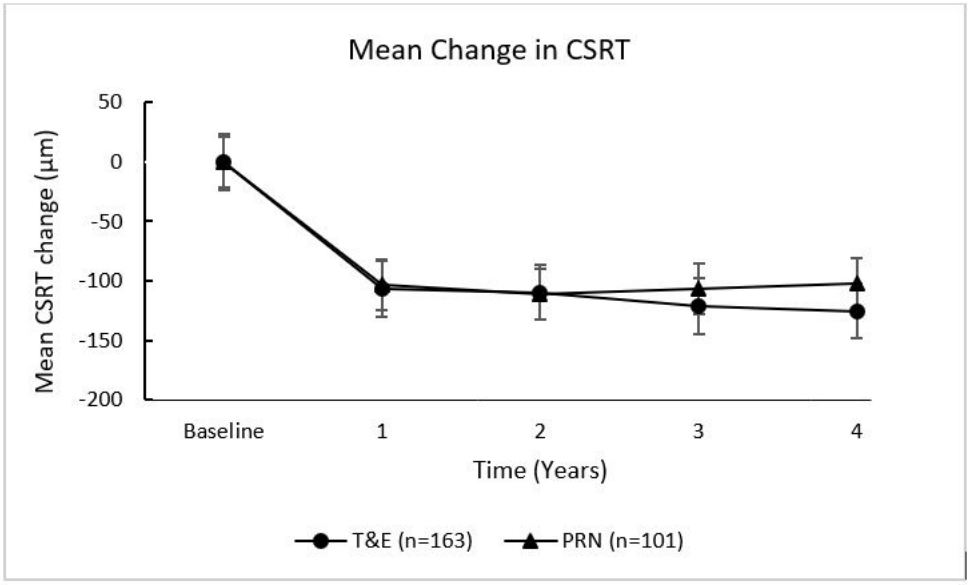




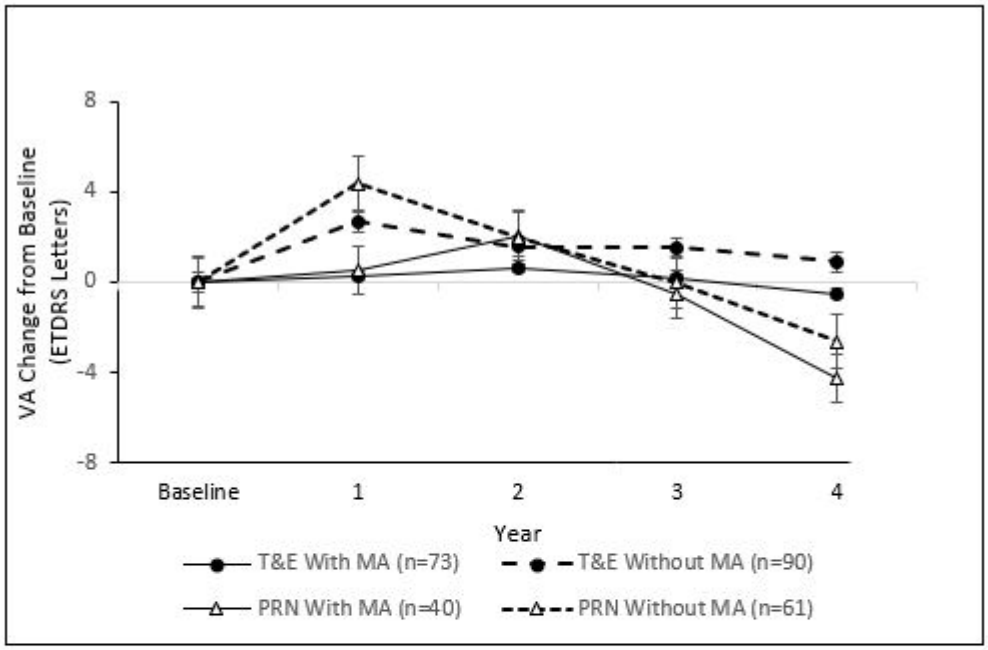








A.


VA Change from Baseline (ETDRS Letters)
8
4
0
-4
-8
Baseline
1
2
3
4
Year
T&E With MA (n=73)
T&E Without MA (n=90)
PRN With MA (n=40)
PRN Without MA (n=61)

B.

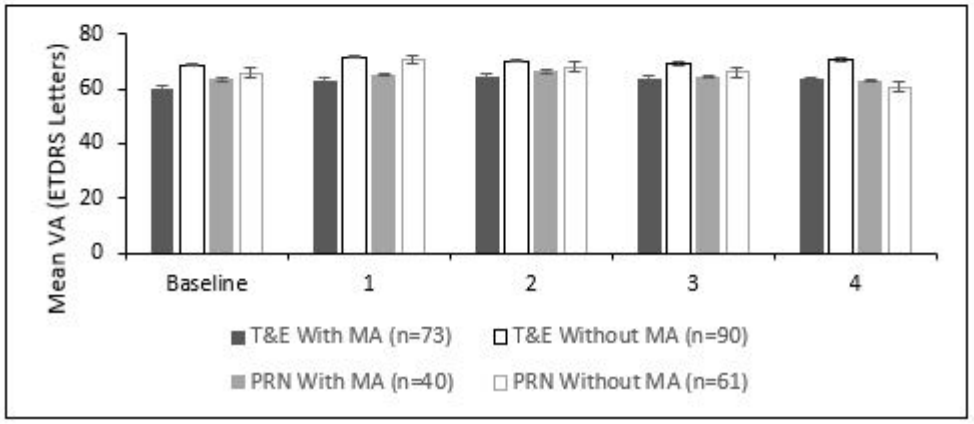

Mean VA (ETDRS Letters)
80
60
40
20
0
Baseline
1
2
3
4
T&E With MA (n=73)
T&E Without MA (n=90)
PRN With MA (n=40)
PRN Without MA (n=61)

Table 1. Baseline Characteristics of Included Patients

	PRN (n=101)	T&E (n=163)	*P* Value
Age, years	74.3 ± 8.4	76.9 ± 8.8	0.33
VA (ETDRS letters)	65.5 ± 14.7	66.9 ± 14.4	0.44
CMT (µm)	416.6 ± 136.5	410.2 ± 105.5	0.67
MA at diagnosis	20 (20%)	39 (24%)	0.45
Unifocal	7 (35%)	11 (28%)	0.09
Multifocal	13 (65%)	28 (72%)	0.08
Foveal	12 (60%)	22 (56%)	0.82
Extrafoveal	8 (40%)	17 (44%)	0.81
MA lesion size (mm^2)	0.8 ± 0.76	1.9 ± 1.9	0.014
Reticular Pseudodrusen	15 (15%)	19 (12%)	0.18
Drusen	57 (56%)	113 (69%)	0.051
Subretinal fibrosis	4 (4%)	6 (4%)	0.91
Gender			0.019
Male	35 (35%)	81 (50%)	
Female	66 (66%)	82 (50%)	
Laterality			0.269
Right	43 (43%)	78 (48%)	
Left	58 (57%)	85 (52%)	
CNV lesion type			0.43
Type 1	61 (60%)	86 (53%)	
Type 2	17 (17%)	30 (18%)	
Type 3 (RAP)	14 (14%)	22 (13%)	
PCV	9 (9%)	15 (9%)	
Lens Status			0.06
Phakic	72(71%)	83 (51%)	
Pseudophakic	29 (29%)	80 (49%)	
History of PDT/Laser	8 (8%)	8 (5%)	0.53

CMT, central macular thickness; CNV, choroidal neovascular membrane; ETDRS, early treatment of diabetic retinopathy score; MA, macular atrophy; PCV, polypoidal choroidal vasculopathy; PDT, photodynamic therapy; RAP retinal angiomatous proliferation; VA, visual acuity