UK AMD/DR EMR REPORT IX: comparative effectiveness of predominantly as needed (PRN) ranibizumab versus continuous aflibercept in UK clinical practice

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ABSTRACT

Aims To compare the effectiveness of continuous aflibercept versus pro re nata (PRN) ranibizumab therapy for neovascular age-related macular degeneration (nAMD).

Methods Multicentre, national electronic medical record (EMR) study on treatment naive nAMD eyes undergoing PRN ranibizumab or continuous (fixed or treat and extend (F/TE)) aflibercept from 21 UK hospitals. Anonymised data were extracted, and eyes were matched on age, gender, starting visual acuity (VA) and year of starting treatment. Primary outcome was change in vision at 1 year.

Results 1884 eyes (942 eyes in each group) were included. At year 1, patients on PRN ranibizumab gained 1.6 ETDRS (Early Treatment Diabetic Retinopathy Study) letters (95% CI 0.5 to 2.7, p=0.004), while patients on F/TE aflibercept gained 6.1 letters (95% CI 5.1 to 7.1, p=2.2e-16). Change in vision at 1 year of the F/TE aflibercept group was 4.1 letters higher (95% CI 2.5 to 5.8, p=1.3e-06) compared with the PRN ranibizumab group after adjusting for age, starting VA, gender and year of starting therapy. The F/TE aflibercept group had significantly more injections compared with the PRN ranibizumab group (7.0 vs 5.8, p<2.2e-16), but required less clinic visits than the PRN ranibizumab group (10.8 vs 9.0, p<2.2e-16). Cost-effectiveness analysis showed an incremental cost-effectiveness ratio of 58 047.14 GBP/quality-adjusted life year for continuous aflibercept over PRN ranibizumab.

Conclusion Aflibercept achieved greater VA gains at 1 year than ranibizumab. The observed VA differences are small and likely to be related to more frequent treatment with aflibercept, suggesting that ranibizumab should also be delivered by F/TE posology.

INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is characterised by choroidal neovascularisation (CNV), which is responsible for the majority of visual loss in AMD.[1] Treatment of CNV primarily lies in reducing the levels of vascular endothelial growth factor-A (VEGF-A), a key mediator in CNV development and activity.

Currently, three intravitreal inhibitors of VEGF are routinely used in clinical practice. Ranibizumab (Lucentis; Genentech, South San Francisco, California, USA), the first Food and Drug Administration-approved therapy that results in improvement of vision in nAMD, is a humanised monoclonal antibody fragment (Fc) that binds all isoforms of VEGF-A.[2] The 'low-cost alternative,'[3] bevacizumab (Avastin; Genentech), is a larger, humanised complete antibody against VEGF-A and is widely used worldwide. Five years after the approval of ranibizumab, aflibercept (Eylea; Regeneron, Tarrytown, New York, USA), a fusion protein of human VEGF receptors 1 and 2 attached to Fc of human immunoglobulin G, became available.[4]

In the UK, intravitreal injections of anti-VEGF drugs are standard therapy to treat nAMD. The National Institute for Health and Care Excellence (NICE) approved the use of ranibizumab in August 2008,[5] leading to almost exclusive usage of ranibizumab (three plus PRN) for nAMD in the UK National Health Service (NHS) until the addition of aflibercept in 2013 (3 monthly loading and then fixed 2 monthly for the first year). Currently, no difference in eligibility criteria exists between the two drugs. Recently, an optional but commonly adopted change in posology allows for a more flexible delivery of ranibizumab to a treat-to-stability approach followed by treat and extend (TE).

No randomised controlled clinical trial has established significant differences in efficacy between ranibizumab and aflibercept for treating nAMD. However, outcomes in clinical practice have frequently been shown to fail to match the results in clinical trials, which is likely to be due to differences in eligibility criteria and the dosing schedule that is actually delivered. In addition, the effect of different posologies in nAMD treatment has not been studied with large, real-world data. In the UK NHS, patients are eligible to receive either ranibizumab or aflibercept without any cost burden to either physician or patient thus providing a non-biased comparison. Indeed, many centres switched en bloc from a three plus PRN (PRN) posology with ranibizumab to continuous dosing (3 monthly injections followed by 2 monthly) or fixed or treat and extend (F/TE) with aflibercept after aflibercept became available in 2013, whereas other centres continued with PRN ranibizumab.

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Thus, UK data sets provide rich clinical data of the real-world outcomes of patients who undergo either ranibizumab or aflibercept in varying posologies. In this study, we have compared the visual outcomes of patients receiving PRN ranibizumab versus F/TE aflibercept treatment regimen.

METHODS

Electronic medical record data source

Anonymised data were extracted from the electronic medical record (EMR) system (Medisoft Ophthalmology; Medisoft, Leeds, UK) of 20 UK centres and from OpenEyes at Moorfields. The Caldicott Guardian (responsible nominee for data protection) gave approval for anonymised data extraction. Anonymised database analyses of this type do not require ethical permission as they are viewed as audit or service evaluation (see http://www.hra.nhs.uk/research-community/before-you-apply/determine-whether-your-study-is-research/). This study was conducted in accordance with the Declaration of Helsinki and the UK's Data Protection Act. Medisoft Ophthalmology is an ophthalmology EMR system that has been integrated in many hospitals in UK. The medical retina module has a structured data set for the management of nAMD that allows the rapid pooling of the data fields collected. This data set was defined and set up before the date of first data collection into this study. OpenEyes (www.openeyes.org.uk) is an open-source ophthalmology EMR system being used at Moorfields Eye Hospital and has a simplified, structured data set for patients receiving intravitreal injections. Although the Medisoft EMR allowed for a more granular capture of data that could potentially allow for more complex analysis, for the purposes of this study OpenEyes allowed for a capture of a minimum data set to accomplish this analysis. Data collected at all sites using both Medisoft Ophthalmology and OpenEyes included VA for each eye (and the method of measurement) and treatment if required (with procedure details and complications).

Data collection and variables

Treatment naive eyes were identified with the diagnosis of exudative age-related macular degeneration. For inclusion in this report, the eyes were required to have at least 1 year of follow-up data as well as treatment monotherapy with either ranibizumab or aflibercept. In this report, the 'best-measured VA' was the best VA with refraction or habitual correction and/or pinhole as measured on an Early Treatment Diabetic Retinopathy Study (ETDRS) chart and expressed as ETDRS letters, which is the mandated way of collecting visual acuity (VA) in the UK for anti-VEGF treated patients. All analyses were performed using ETDRS letters. Data variables also extracted included age, gender, site of treatment, dates of assessment visits and dates of intravitreal therapy.

Missing data

For patients where data were not available for a particular visit or had been lost to follow-up no missing value substitutions were performed. The only exception to this rule was baseline VA as some treatment centres brought patients back for a two-stop service: assessment on the first visit followed by injection on the second visit, and did not repeat VA measurements on the date of the first injection, which was always performed within 3 weeks. This was therefore not missing data per se but reflects variation in treatment delivery.

Statistical methods

For each eye treated with aflibercept, a raibizumab-treated eye was matched to another patient with similar age within 5 years, the same gender, starting VA within 5 ETDRS letters and the date of starting therapy within 1 year. For patients who were seen in clinic and received anti-VEGF in a subsequent visit, we accounted for two stop visits and counted these as one stop each. Each matching was performed using a pseudorandom number generator to pick a patient treated with ranibizumab from the set of patients matching the criteria. Each picked ranibizumab treated eye was ensured to be unique, and the order of aflibercept patients considered was also pseudorandomised. Continuous variables were analysed with a linear model. A multivariate linear model was created to assess the effect of the drug on the change in VA adjusted for age, gender, starting year and starting VA at 1 year. The starting VA stratification cut-offs were chosen a priori without knowledge of the outcome.

Cost-effectiveness and incremental cost-effectiveness ratio (ICER) analysis was performed using utilities from Brown *et al*[6] and costs for ranibizumab and aflibercept were set at 742.17 GBP and 816.00 GBP, respectively. Non-injection visit cost was estimated at 60.00 GBP. Injection visit cost was estimated at 315.00 GBP by combining the cost of an evaluation visit with cost of administrating the injection. These costs were taken from the costing template for unit costs used by NICE.[7] All statistics were performed using R version 3.2.5 (http://www.r-project.org).

RESULTS

A total of 942 eyes in each treatment group were matched on age, gender, starting VA and year of starting therapy. No patient received different anti-VEGF (ranibizumab or aflibercept) for two eyes. The baseline demographic characteristics of the patients are shown in table 1. No significant differences were noted in the baseline characteristics between the two groups other than the year of starting therapy (2013.24 vs 2013.93), which was highly statistically significant. A total of 1090 study eyes originated from Medisoft data set and 794 study eyes from OpenEyes data set.

At year 1, eyes on PRN ranibizumab gained 1.59 letters (95% CI 0.5 to 2.7, p=0.004), while eyes on F/TE aflibercept gained 6.10 letters (95% CI 5.1 to 7.1, p=2.2e-16). Mean visual acuities are shown for each month with the number of eyes in each group in figure 1. By multivariate modelling at month 12 (52 weeks), there was a statistically significant difference of 4.1 ETDRS letters (95% CI 2.5 to 5.8, p=1.3e-06) in the aflibercept F/TE group compared with the ranibizumab PRN group after adjusting for age, starting VA, gender and year of starting therapy (table 2). After stratifying by baseline VA groups, there were statistically significant differences at 12 months of 4.0 ETDRS letters (95% CI 1.6 to 6.4, p=0.001) in the 50–69 ETDRS letter group and 6.8 ETDRS letters (95% CI 3.0 to 10.6, p=0.0005) in

Table 1 Baseline characteristics

	Ranibizumab	Aflibercept	p Value
No of eyes	942	942	
Right eyes, n (%)	480 (47.77)	500 (53.08)	0.38
Female, n (%)	598 (63.48)	598 (63.48)	1.00
Mean visual acuity at presentation, ETDRS letters (SD)	55.01 (15.63)	54.89 (15.99)	0.88
Mean year of starting therapy (SD)	2013.24 (0.59)	2013.93 (0.50)	2.2e-16*

*p-value <0.05.
ETDRS, Early Treatment Diabetic Retinopathy Study.

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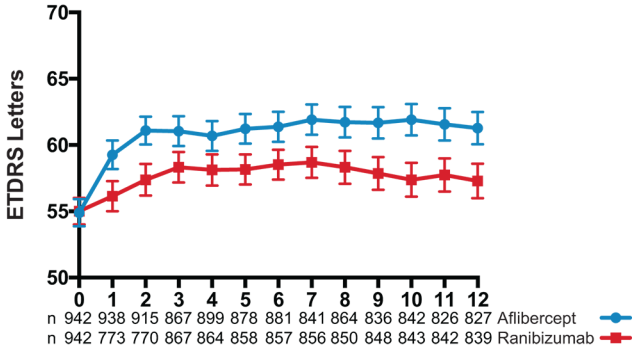

Figure 1 Monthly visual acuity outcomes in pro re nata ranibizumab versus fixed or treat and extend aflibercept matched by gender, age, starting visual acuity and year of starting therapy. Mean visual acuities for each month are shown with 95% CIs as error bars. The number of patients with follow-up is shown underneath for each month. ETDRS, Early Treatment Diabetic Retinopathy Study.

the 30–49 letter group after adjusting for age, gender and year of starting therapy (figure 2 and table 3).

In terms of utilisations, the F/TE aflibercept group had statistically significantly more injections in 1 year compared with the PRN ranibizumab group with an average of 7.0 injections and 5.8 injections, respectively (mean difference: 1.1 injections, 95% CI 1.0 to 1.3, p<2.2e-16). However, the number of clinic visits during 1 year was statistically significantly higher for the PRN ranibizumab group compared with the F/TE aflibercept group, 10.8 visits versus 8.95 visits (mean difference: 1.9 visits, 95% CI 1.6 to 2.1, p<2.2e-16) (figure 3).

Stratification of the utilisation by starting VA groups showed similar trends in both clinic visits and number of injections. In all four starting VA groups, there were statistically significantly more injections given in the aflibercept group compared with the ranibizumab group (mean difference range: 1.0 to 1.2, p values range: 2.2e-16 to 0.009). In all starting VA groups except for patients with less than 30 ETDRS letters (mean difference: 1.00, 95% CI −0.1 to 2.1, p=0.068), there were statistically significant more clinic visits in the ranibizumab group compared with the aflibercept group (mean difference range: 1.7 to 2.0, p values range: 2.2e-16 to 3.0e-09) (figure 4).

Cost-effectiveness analysis for the PRN ranibizumab and F/TE aflibercept groups showed an average cost of 5633.55 GBP and 6987.69 GBP, respectively. The 1 year utilities for the ranibizumab and the aflibercept groups were 0.67 quality-adjusted life year (QALY) and 0.69 QALY, respectively. The calculated ICER for aflibercept was 58 047 GBP/QALY. Using TA 294 guidelines, aflibercept dominated ranibizumab assuming 0% discount in either drug.[7] The ICER in the better and the worse seeing eye models were 261 432 GBP/QALY and 1 692 511 GBP/QALY, respectively. However, the evidence review group (ERG) incorporated the confidential discount applied to the list price of aflibercept; therefore, a direct comparison with the ICERs in their study cannot be made. In addition, our study was not a binocular eye model.

Table 2 Change in visual acuity at 1 year from baseline by treatment adjusted for starting visual acuity, age, gender and year of starting therapy by multivariate modelling

Variable	Beta	95% CI	p Value
Drug (posology)			
Ranibizumab (three plus PRN)	ref		
Aflibercept (fixed dosing or treat and extend)	4.15	2.48 to 5.82	1.25e-06*
Starting visual acuity	−0.31	−0.35 to −0.26	2e-16*
Age	−0.24	−0.33 to −0.15	3.89e-07*
Female	−0.95	−2.43 to 0.52	0.21
Year of starting therapy	0.23	−1.08 to 1.53	0.73

*p-value <0.05.
PRN, pro re nata.

DISCUSSION

In this study, we demonstrated that the 1-year VA outcome is statistically significantly higher with fixed dosing or treat and extend aflibercept injections than three plus PRN ranibizumab therapy. This difference was significant for starting VA of 30–49 (20/252–20/105) and 50–69 ETDRS letters (20/100–20/42) with the worse vision group leading to a larger improvement. Similar trends were found in patients with better than 69 (>20/42) or worse than 30 ETDRS letters (<20/252) but did not reach a statistical significance.

The different outcomes for VA of the two drugs in this study must either be related to differences between the two drug's actions or due to the different delivery strategies. Although there are different binding characteristics of the two drugs to VEGF, the pivotal trials did not reveal superiority of one drug when given in fixed dosing delivery for treating nAMD.[8] In addition, a recent study of real-world data from 394 eyes with nAMD revealed no significant difference in VA outcomes at 12 months between ranibizumab and aflibercept group when given in similar intervals.[9] Therefore, despite the differences in the two compounds, our results could reflect differences in the posologies of the two treatment arms rather than different efficacies of two drugs. Not surprisingly, patients in the aflibercept arm had more injections (mean=7.0 vs 5.8) but fewer clinic visits (mean=9.0 vs 10.9) than ranibizumab. Variable dosing regimen of ranibizumab resulting in comparable visual outcomes with a fewer number of injections compared with randomised controlled trials has been reported previously.[10] In comparison with PRN dosing, fixed or TE posologies have been shown to be associated with better visual outcomes: the 2 years of Comparison of Age-related Macular Degeneration Treatments Trial (CATT) showed that mean VA gain was greater for monthly than for as-needed treatment (−2.4 letters, 95% CI −4.8 to −0.1, p=0.046) in either ranibizumab or bevacizumab therapy regardless of when PRN posology was implemented.[11] Hatz *et al* demonstrated that the mean change in BCVA from baseline to 1 year was significantly greater in the F/TE than the PRN group (0.18 vs 0.17, p<0.001) in 140 treatment naive patients with nAMD.[12]

Our study showed a difference of 4.2 ETDRS letters in VA at 1 year between the two therapies delivered by PRN versus F/TE. Overall, the patients on PRN ranibizumab gained 1.6 letters, while patients on F/TE aflibercept gained 6.1 letters on year 1. The difference was higher in the worse baseline VA group (6.8 letters in 30–49 ETDRS group) compared with the better VA group (4.0 letters in 50–69 ETDRS group). Whether approximately 4 letters of difference is clinically meaningful is debatable as it is within the non-inferiority margins used in clinical trials such as CATT of 5 letters.[13] Nevertheless, more significant gain in VA in the worse baseline VA group was noted in our study. We do not know whether the difference of 6.8 letters are clinically significant in patients who are already not seeing well, but this effect is much higher than the differences seen in other trials such as CATT.[13] In addition, the stability of this difference at a later

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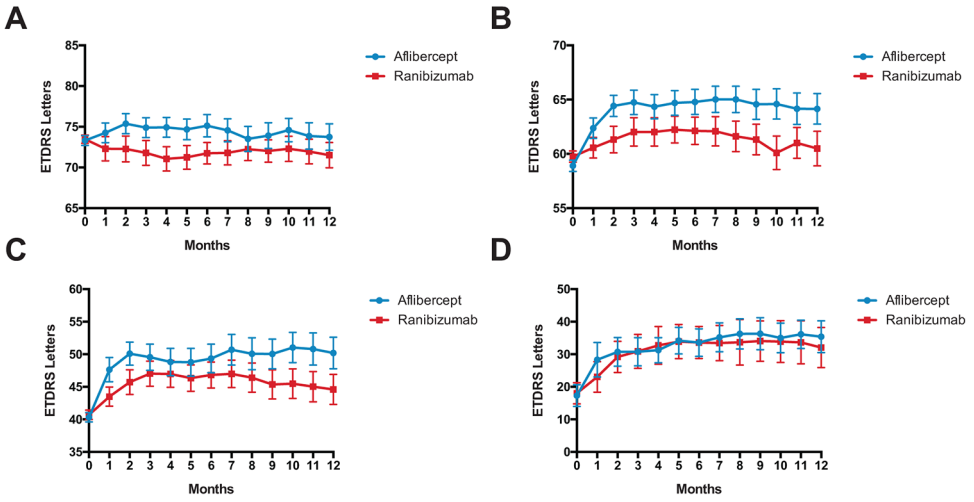

Figure 2 Monthly visual acuity outcomes stratified by starting visual acuity in pro re nata ranibizumab versus fixed or treat and extend aflibercept matched by gender, age, starting visual acuity and year of starting therapy. Mean visual acuities for each month are shown with 95% CIs as error bars. Starting visual acuity was stratified by (A) ≥70 ETDRS letters, (B) 50–69 ETDRS letters, (C) 30–49 ETDRS letters and (D) <30 ETDRS letters. ETDRS, Early Treatment Diabetic Retinopathy Study.

time period (eg, 2 years) is unknown. The year 1 result of PIER study showed mean change of −0.2 letters in 61 patients who received 3 monthly 0.5 mg of ranibizumab followed by every 3 month dosing. Patients gained 4.3 letters at the end of 3 month dosing but continued to decline during quarterly dosing.[14] Interestingly, compared with the PIER study, the visual decline in our study was lower in both ranibizumab and aflibercept group. Taking into account the varying visual outcomes throughout different studies, when choosing a therapy and posology, other variables should be considered, including: the total number of clinic visits, cost-effectiveness and factors that may be applicable to individual patients such as disease activity in the fellow eye. The ICER for aflibercept over ranibizumab in our study was 58 047.14 GBP/QALY, which is considerably above the ICER thresholds for funding in most countries. However, local pricing of the drug and delivery will likely have an impact on ICER.

Previous studies suggest no significant difference in the real-world effectiveness of ranibizumab versus aflibercept. Hata *et al* reviewed the records of 216 treatment naive patients who underwent 3 monthly aflibercept or ranibizumab in Japan.[15] The VA or foveal thickness at 1 month after the third injection did not significantly differ between the two treatment arms. A recent study of 394 eyes (197 with ranibizumab and 197 with aflibercept) showed no significant difference in the visual outcome at year 1.[9] The patients were treated with either monthly, PRN or TE regimen, but the particular posology for each patient was unknown in 50% of the cases. These study findings further suggest that the mild difference that we observed between two anti-VEGF groups most likely represent the different effectiveness of treatment frequency.

Our study has several limitations. The study only includes UK hospitals that use an EMR system; however, our data are from 21 different centres, which likely assimilates any inter-centre variation that exists. The difference in posologies used for the two drugs (PRN for ranibizumab vs F/TE for aflibercept) reflects the treatment pattern that existed in the UK NHS at the time of data collection. In 2014, the label for ranibizumab was changed to allow more flexible and personalised treatment including treat and extend delivery; thus our results may not be applicable for patients undergoing different treatment protocols of either drug. However, this study provides real-world data that reflect different clinical practice patterns. The number of visits for the F/TE group was not the same as the number of injections, as might be expected in a strict F/TE posology. The reasons for the discrepancy include bilateral injections in which only one eye was treated in each visit, visits for monitoring adverse events or unrelated eye visits. When we excluded patients undergoing bilateral injections, the average difference in number of injections and visits was less than 1, in keeping with other reports on T/E regimen in the real world.[16] The lack of OCT data is also

Table 3 Change in visual acuity at 1 year from baseline by treatment stratified by starting visual acuity and adjusted for age, gender and year of starting therapy by multivariate modelling

	Aflibercept compared with ranibizumab			
Starting visual acuity	n	Beta	95% CI	p Value
≥70 ETDRS letters	348	2.06	−0.56 to 4.67	0.12
50 to 69 ETDRS letters	822	3.99	1.61 to 6.37	0.001*
30 to 49 ETDRS letters	410	6.82	3.00 to 10.64	0.0005*
<30 ETDRS letters	88	7.87	−3.13 to 18.87	0.17

*p-value <0.05. ETDRS, Early Treatment Diabetic Retinopathy Study.

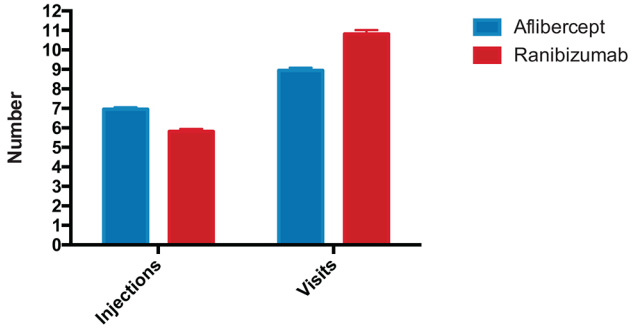

Figure 3 Utilisation of injections and visits for pro re nata ranibizumab versus fixed or treat and extend aflibercept. Mean number of injections and visits in year 1 are shown with 95% CIs as error bars.

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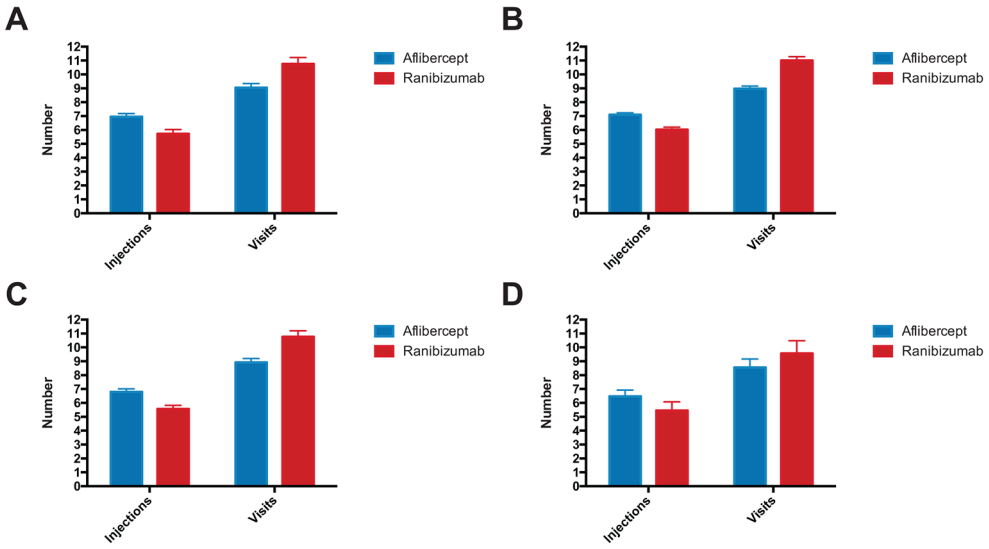

Figure 4 Utilisation of injections and visits stratified by baseline visual acuities for pro re nata ranibizumab versus fixed or treat and extend aflibercept. Mean number of injections and visits in year 1 are shown with 95% CIs as error bars. Starting visual acuity was stratified by (A) ≥70 ETDRS letters, (B) 50–69 ETDRS letters, (C) 30–49 ETDRS letters and (D) <30 ETDRS letters. ETDRS, Early Treatment Diabetic Retinopathy Study.

a limitation. In addition, selection bias or location effect could have occurred due to OpenEyes data set coming from Moorfields Eye Hospital only while the rest of the centres contributing to Medisoft data. Finally, our data only included 1 year results; thus, whether these results are maintained at a later time periods is unknown.

To our best knowledge, this is the largest study reporting the real-world visual outcomes of patients on varying posology of ranibizumab versus aflibercept therapy. Our results demonstrate that 1 year visual outcomes of fixed dosing or treat and extend aflibercept therapy is superior to three plus PRN ranibizumab therapy, most likely due to the difference in posology rather than drugs. Crude outcomes of ranibizumab therapy in Australia with a F/TE approach suggests superiority to three plus PRN, used until recently in the UK, although baseline differences would need to be explored to support this assertion.[17 18] The cost-effectiveness of two posologies and impact on clinic capacity are also important considerations when deciding which drug and posology to use.

In summary, F/TE aflibercept achieved greater VA gain at 1 year than predominantly PRN ranibizumab but required a greater number of injections. The VA differences observed in this study are likely to be related to the posology of F/TE than differences in the drug compounds that deliver a greater average number of treatments per patient in a real-world setting. Hence, our results have important clinical implications, as F/TE is likely to become the standard of care for aflibercept, ranibizumab and bevacizumab when treating nAMD. The data suggest that patients on PRN ranibizumab therapy should consider shifting to a continuous (F/TE) posology.

Contributors All the authors have contributed to the planning, conduct and reporting of the work described in the article.

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Competing interests AYL has received grants from Novartis, Microsoft and Nvidia. RLJ is the Medical Director of Medisoft Limited, which developed the EMR from which data were extracted. RH has received grants and speaker fees from Novartis, Allergan, Bayer and Ellex. LD has received speaker fees from Novartis, Bayer, Allergan and Alimera. CAE has received speaker fees from Heidelberg Engineering and Haag-Streit UK. AT has served on Advisory Boards for Allergan, Bayer, Genetech, GlaxoSmithKline, Novartis and Roche.

Patient consent Only anonymised database analyses were performed and hence consent was not required from the patients.

Provenance and peer review Not commissioned; externally peer reviewed.

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