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RETINAL DISORDERS

A pharmacoepidemiologic study of ranibizumab and aflibercept use 2013–2016. The Fight Retinal Blindness! Project

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Abstract

Introduction To report 12-month pharmacoepidemiologic data on aflibercept and ranibizumab use in treatment-naïve eyes with neovascular age-related macular degeneration (nAMD).

Methods Participants were treatment-naïve eyes with nAMD tracked by the Fight Retinal Blindness! registry starting therapy with aflibercept or ranibizumab treatment between January 1st, 2013 and 31st December, 2016. Demographic and clinical characteristics were compared between treatment groups.

Results During the study period, 689 eyes initiated treatment with ranibizumab compared to 568 with aflibercept. We found a similar rate of use of both drugs. Ranibizumab-treated patients were older than aflibercept-treated patients (overall mean [SD] 82.0 [8.4] vs. 78.6 [8.1], $P < 0.001$). Median (Q1, Q3) lesion size was significantly larger in aflibercept-treated patients (2450 μm [1242, 3000]) compared with ranibizumab patients (2000 μm [1148, 2890], $P = 0.008$). Eyes treated with ranibizumab and aflibercept received a similar mean number of injections in the first 3 months (3.1 [0.7] vs. 3.0 [0.6]; $P = 0.233$) and at 12 months (7.3 [2.4] vs. 7.2 [2.2]; $P = 0.139$). The 12-month switching rates from 2013 onwards for eyes completing 12 months of follow-up were much higher for switching from ranibizumab to aflibercept (19.2%) compared with switching from aflibercept to ranibizumab (5.4%). The proportion of eyes that did not complete 12 months of treatment was 23.2% for ranibizumab and 22.2% for aflibercept-treated groups.

Conclusion A similar rate of use for ranibizumab and aflibercept among Australian practitioners was observed between 2013 and 2016. Ranibizumab was used more often in older patients while aflibercept tended to be used more often in eyes with larger lesions.

Keywords Ranibizumab · Aflibercept · Neovascular age-related macular degeneration · Pharmacoepidemiology

Introduction

Age-related macular degeneration (AMD) is a leading cause of blindness in developed countries [1] and accounts for 7% of all blindness worldwide [2]. The worldwide prevalence of late AMD has been estimated to 0.4% [3]. Following the unprecedented improvements in visual outcomes demonstrated in several pivotal randomised clinical trials [4–7], vascular endothelial growth factor (VEGF) inhibitors are now used widely in clinical practice to treat the neovascular form of age-related macular degeneration (nAMD).

The two drugs licenced in Australia to treat nAMD are ranibizumab and aflibercept. Ranibizumab (Lucentis®) received FDA approval for nAMD treatment in 2006 [8, 9]. Both are freely available for the same indication. Data from US Medicare databases found that the number of injections of ranibizumab began to decline in 2011 [10] with important regional variations and multifactorial reasons [11]. The use of off label bevacizumab [11] or the FDA approval for aflibercept (Eylea®) in 2011 [12] may have contributed to this trend.

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Data regarding the binding affinity of ranibizumab and aflibercept to VEGF have yielded conflicting results in in vitro studies [13–16]. There are no randomised clinical trial (RCT) that have compared aflibercept with ranibizumab for nAMD apart from the pivotal phase III RCTs of aflibercept [7, 17]. Our recent analysis of data from routine clinical practice did not find any significant difference in 12-month visual acuity outcomes and durability, as measured by average number of injections, between ranibizumab and aflibercept [18].

The aim of the current study was to examine the use of ranibizumab and aflibercept as the initial treatment for nAMD in Australian centres participating in the Fight Retinal Blindness! (FRB!) database from 2013 until 2016. Secondary objectives were to report the baseline demographic and clinical characteristics between treatment groups, 12-month switching rates between treatments, treatment frequency and 12-month lost to follow-up rates.

A clear understanding of the manner in which these treatments are used will allow insights into the perceived effectiveness of the drugs from the treating clinician's perspective. Determining the use of aflibercept and the time taken for the relative market share of the two treatments to stabilise will invite further questions regarding the pharmacoepidemiology of these competing treatments in the real-world setting.

Methods

Design and setting

This was a retrospective observational study comparing the use of ranibizumab and aflibercept in Australia for nAMD in treatment-naïve eyes in routine clinical practice from the FRB! database. The details of the FRB! database have been published elsewhere [19]. At the time the analysis was conducted, there were 89 unique practices that contributed data to the registry, including practices from Australia, New Zealand, Netherlands, Singapore, Spain and Switzerland. Data were obtained prospectively from each clinical visit and included the number of letters read on a logarithm of the minimum angle (LogMAR) of resolution visual acuity (VA) chart (best of uncorrected, corrected or pin hole); treatment given, if any, and ocular adverse events. Demographic characteristics (age, gender), angiographic lesion size (measured as the greatest linear dimension in micrometres) and type, as determined using fundus fluorescein angiography, and whether the eye had received prior treatment were recorded at the baseline visit. Treatment decisions, including choice of drug, and injection frequency were at the discretion of the physician in consultation with the patient, thereby reflecting real-world practice. Institutional ethics approval was obtained from the Human Research Ethics Committees of the University of Sydney, the Royal Victorian Eye and Ear Hospital, the Royal Australian and New Zealand College of Ophthalmologists. Ethics committees in Australia approved the use of "opt out" patient consent. The research described adhered to the tenets of the Declaration of Helsinki.

Study population

The study population consisted of treatment-naïve eyes initiating therapy with either ranibizumab or aflibercept for the treatment of nAMD from 1st January 2013 to 31st December 2016 at Australian clinics participating in the FRB! registry. Eyes that had received prior treatment were excluded to determine the usage of aflibercept and ranibizumab as a first-line treatment option for nAMD. Aflibercept was reimbursed by the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia in December 2012. Eyes must have received at least three injections, with a maximum time between two consecutive visits of 180 days to establish treatment initiation and regular ongoing treatment, and to avoid potential confounding of treatment frequency that may arise due to unrelated patient circumstances. Eyes were grouped as initiating treatment on ranibizumab or aflibercept based on the drug given at the first injection.

Outcomes reporting switching rates and injections required eyes to have at least 12 months of follow-up (completers) and to have initiated treatment from 1st January 2013 to 1st October 2015, thus allowing up to 3 months for a follow-up visit for eyes initiating treatment in October 2015. Switching was defined as receiving ≥ 2 consecutive injections of the other treatment drug prior to completing 12 months of follow-up. Non-completers (lost to follow-up) were defined as eyes without a follow-up visit at 12 months or later after initiating treatment.

Study outcomes

The primary outcome measure was the proportion of eyes receiving an initial treatment of ranibizumab vs. aflibercept in Australian practices over time. Secondary outcomes include a comparison of baseline demographic and clinical characteristics between treatment groups by year of treatment initiation, variation in choice of initial treatment between practices, 12-month switching rates between treatments, treatment frequency and 12-month lost to follow-up rates.

Statistical analyses

Descriptive statistics included mean (SD), median (first and third quartiles [Q1, Q3]) and percentages where appropriate. Comparison of demographic characteristics between treatment groups were conducted using Student's *t*, Wilcoxon rank sum and chi-square tests where appropriate.

The number of injections received at 3 and 12 months was compared between treatment groups using Poisson regression models adjusted on age, baseline VA, lesion size and type (fixed-effects) and practice (random-effect) with the logarithm of days follow-up included as an offset variable. Time to switching and lost to follow-up were analysed using Kaplan-Meier survival curves and compared between treatment groups using Cox proportional-hazards regression models adjusted on age, baseline VA, lesion size and type (fixed-effects) and practice (random-effect). All analyses were performed using R V.3.3.2 with the *lme4* package (V.1.1.-12) for regression analysis, the *survival* package (V.2.40–1) for Kaplan-Meier analyses and the *coxme* package (V.2.2-5) for Cox proportional-hazards models [20].

Results

Demographic characteristics

Overall, data from 44 practitioners from 42 practices in Australia (out of a possible 61 practices) meeting the inclusion criteria were analysed. The demographic characteristics of eyes by treatment group and year of study entry are summarised in Table 1. The mean age of ranibizumab-treated patients was significantly greater than aflibercept-treated patients (overall mean 82.0 [8.4] vs. 78.6 [8.1]; $P < 0.001$), which was consistent over the duration of the study period (Fig. 1).

Clinical characteristics

There was no significant difference in baseline VA between ranibizumab and aflibercept ($P = 0.396$) or angiographic lesion type ($P = 0.786$; Table 1). Median (Q1, Q3) lesion size was significantly larger in aflibercept-treated patients (2450 μm [1243, 3000]) compared with ranibizumab patients (2000 μm [1148, 2890]; $P = 0.008$; Table 1).

Use of ranibizumab and aflibercept as an initial treatment over time

From 1st January 2013, 689 treatment-naïve eyes initiated treatment with ranibizumab and 568 with aflibercept (Fig. 2). Uptake of the two drugs was balanced until the end of 2013 from which point the uptake of aflibercept tended to be lower than that of ranibizumab but the difference was not statistically significant ($P = 0.367$). There was a somewhat higher treatment initiation rate for ranibizumab over aflibercept in all years from the end of 2012 when aflibercept was first introduced (Fig. 3).

Variation between practices

We studied the use of ranibizumab and aflibercept by the 5 largest contributing Australian practices from the FRB! registries over time (Fig. 4). Treatment choices varied somewhat between practices and changed over time. One practice, consisting of two practitioners, remained at approximately 50% between initiating treatment on ranibizumab and aflibercept suggesting no perceived superiority from prescribers of one drug over the other. Another practice started 81% eyes on aflibercept in 2013, but this proportion steadily declined to 40% in 2015 and was 50% in 2016. Three others initiated treatment predominantly on ranibizumab in 2013 (86, 83 and 69%), but this proportion declined to 42, 52 and 47% in 2015 respectively. However, all three practices returned to treating predominantly with ranibizumab in 2016 (75, 80 and 74% of patients respectively).

Treatment frequency

Eyes treated with ranibizumab and aflibercept received a similar mean [SD] number of injections in the first 3 months of therapy (3.1 [0.7] vs. 3.0 [0.6]; $P = 0.233$) and at 12 months (7.3 [2.4] vs. 7.2 [2.2]; $P = 0.139$).

12-month switching between treatments

The overall 12-month switching rates from 2013 onwards for eyes completing 12 months of follow-up were higher for switching from ranibizumab to aflibercept (19.2%) compared to switching from aflibercept to ranibizumab (5.4%; Fig. 5). Switching rates declined from 23.6% for eyes initiating ranibizumab in 2013 to 16.7% in 2015, and from 5.7% in 2013 to 5.5% in 2015 for eyes initiating aflibercept. The median time (Q1, Q3) to switching was longer for eyes starting on ranibizumab (168 [120, 232] days) compared with aflibercept (109 [67, 214] days; $P < 0.001$). The overall rate of switching back to the initial treatment within 12 months was 1% for ranibizumab and 2% for aflibercept.

12-month non-completion rates

The proportion of eyes lost to follow-up before completing 12 months of treatment was 23.2% for ranibizumab and 22.2% for aflibercept-treated groups (Fig. 6). Median time (Q1, Q3) to loss of follow-up was similar between ranibizumab (185 [133, 266] days) and aflibercept (222 [112, 289] days; $P = 0.902$). Reasons for non-completion were recorded in 28/126 cases and included deceased ($n = 5$), further treatment futile ($n = 7$), patient declining treatment ($n = 7$) and patient going to another doctor not enrolled in the registry ($n = 9$).

Table 1 Comparison of baseline demographic characteristics between ranibizumab (Ran) and aflibercept (Afl) by year of study entry. *P* values comparing ranibizumab vs. aflibercept are presented for the totals across all years

	2013		2014		2015		2016		Total		*P* value
Initial injection	Ran	Afl	Ran	Afl	Ran	Afl	Ran	Afl	Ran	Afl	
Number of eyes	175	137	169	157	191	164	154	110	689	568	
Number of patients	161	131	160	147	185	153	145	106	631	516	
Female (%)	58.3%	59.9%	71.0%	54.8%	60.7%	59.8%	63.6%	54.5%	63.3%	57.4%	0.039
Mean baseline age, years (SD)	82.4 (7.6)	77.6 (7.9)	82.7 (7.7)	78.7 (8.2)	80.9 (9.4)	79.9 (7.7)	82.2 (8.9)	77.9 (8.4)	82.0 (8.4)	78.6 (8.1)	< 0.001
Mean baseline VA (SD)	58.2 (20.0)	60.9 (17.7)	61.5 (18.4)	59 (18.6)	60.6 (18.2)	56.6 (21.6)	61.1 (17.2)	62.4 (17.5)	60.3 (18.5)	59.4 (19.2)	0.396
VA ≥ 70 letters, %	34.9%	38.7%	40.8%	35%	40.8%	34.8%	40.9%	47.3%	39.3%	38.2%	0.745
VA ≤ 35 letters, %	17.1%	11.7%	8.9%	13.4%	9.9%	18.3%	9.1%	8.2%	11.3%	13.4%	0.301
Lesion size, μm (median, Q1, Q3)	2304 (1354, 3103)	2500 (1500, 3000)	2000 (1150, 2561)	2500 (1240, 3000)	2417 (1300, 3000)	2500 (1435, 3178)	1500 (1000, 2500)	2000 (1000, 3000)	2000 (1148, 2890)	2450 (1242, 3000)	0.008
Angiolesion type, %											
Occult	56.6%	50.4%	57.4%	54.1%	50.8%	57.3%	52.6%	45.5%	54.3%	52.5%	0.786
Minimally classic	15.4%	13.1%	8.3%	9.6%	9.4%	8.5%	8.4%	11.8%	10.4%	10.6%	
Predominantly classic	18.9%	27.7%	24.9%	27.4%	30.9%	26.2%	26.6%	20.0%	25.4%	25.7%	
Other	8.6%	6.6%	8.3%	5.7%	6.3%	4.9%	4.5%	4.5%	7.0%	5.5%	
Not Recorded	0.6%	2.2%	1.2%	3.2%	2.6%	3.0%	7.8%	18.2%	2.9%	5.8%	

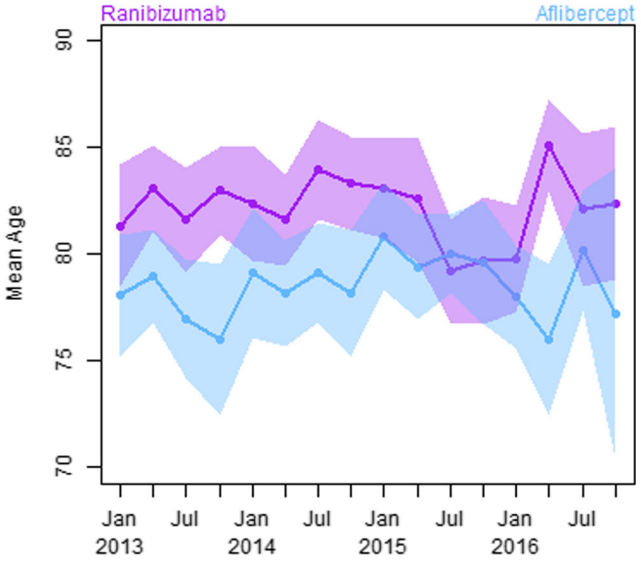

Fig. 1 Mean age of patients initiating treatment on ranibizumab vs. aflibercept over time. The 95% confidence intervals are given by the coloured shading

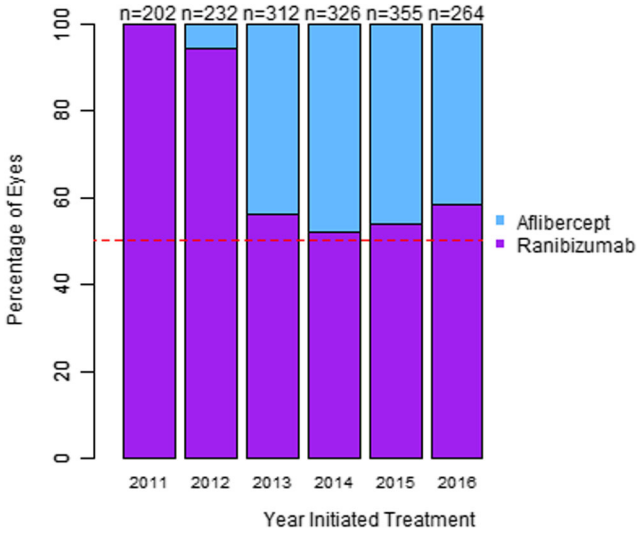

Fig. 3 Proportion of eyes initiating ranibizumab vs. aflibercept over time as a proportion of total eyes entering the study for each year. Total number of eyes for each year are labelled above the bars. Years 2011 and 2012 are shown to highlight the transition as aflibercept was introduced to the Australian market. The red dashed line represents equal (50%) treatment initiation for ranibizumab and aflibercept

Discussion

We studied the utilisation of aflibercept and ranibizumab in a cohort of more than 1000 treatment-naïve eyes with nAMD in Australia from 2013 when aflibercept first became reimbursed. There did not seem to be a significant preference of one drug over the other during the study period. The number of injections and patient visits did not differ significantly between the drugs; however, more prescribers switched treatments from ranibizumab to aflibercept than vice versa. Overall, no clinically relevant difference regarding the utilisation of the two drugs was found, with similar numbers of injections in the first 3 and 12 months after beginning therapy.

Pharmacoepidemiology, according to the International Society for Pharmacoepidemiology, is "the science that applies epidemiologic approaches to studying the use,

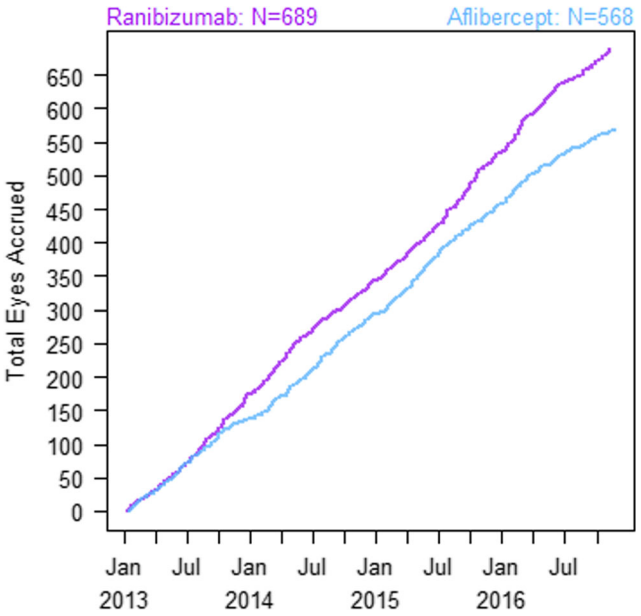

Fig. 2 Use of ranibizumab vs. aflibercept as an initial treatment for nAMD in Australian practices from January 2013 to December 2016. From 1st January 2013, there were 689 treatment-naïve eyes initiating treatment on ranibizumab and 568 with aflibercept. Use between the two drugs was balanced until the end of 2013 from which point the use of aflibercept was trended less but not significant than that of ranibizumab ($P = 0.367$)

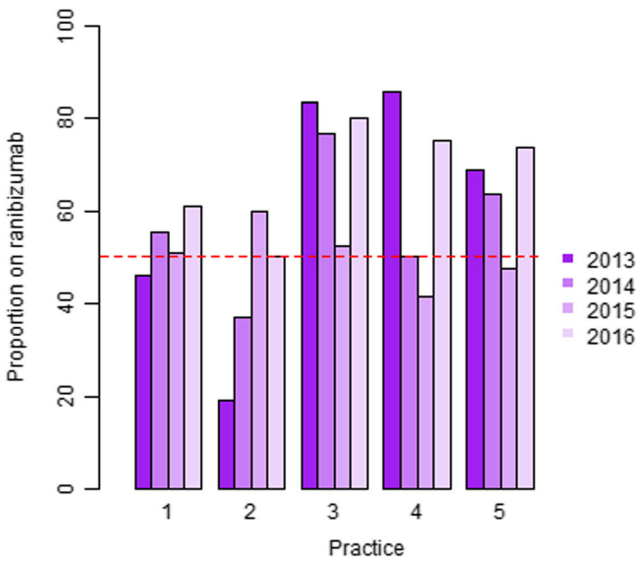

Fig. 4 Proportion of eyes initiating ranibizumab over time for the 5 largest contributing practices in the FRB registry for each year. The red dashed line represents equal (50%) treatment initiation for ranibizumab and aflibercept

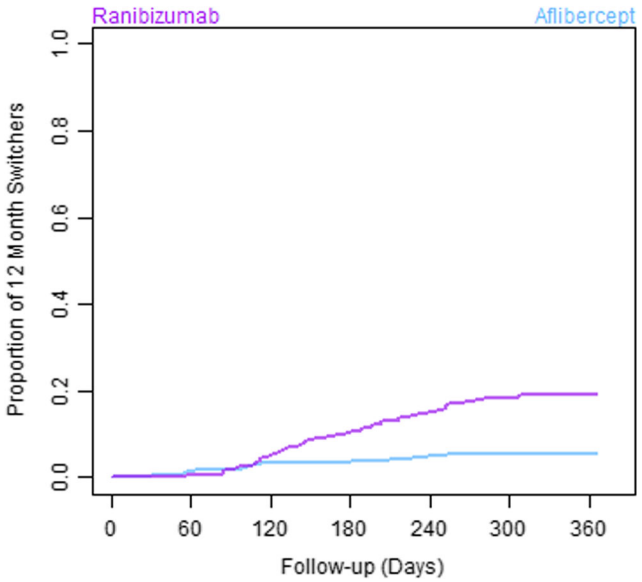

Fig. 5 Kaplan-Meier survival analysis of length of time to switching treatments within 12 months for ranibizumab and aflibercept

effectiveness, value and safety of pharmaceuticals" [21]. Pharmacoepidemioloic studies aim to provide data on how drugs are used in the general population [22].

The approval of a new drug for a specific condition often changes prescription patterns for that condition. A number of factors, some of which are perceived by the prescribing physician, such as superior efficacy, lower rate of side effects and thus better patient compliance, greater ease of use (e.g. no need to monitor liver enzymes or other ancillary tests) or reimbursement policies, may contribute to this. For example, the introduction of new anticoagulants in the USA has resulted in a shift away from warfarin as the first-line drug to other agents in patients with atrial fibrillation. Nearly 100% of patients

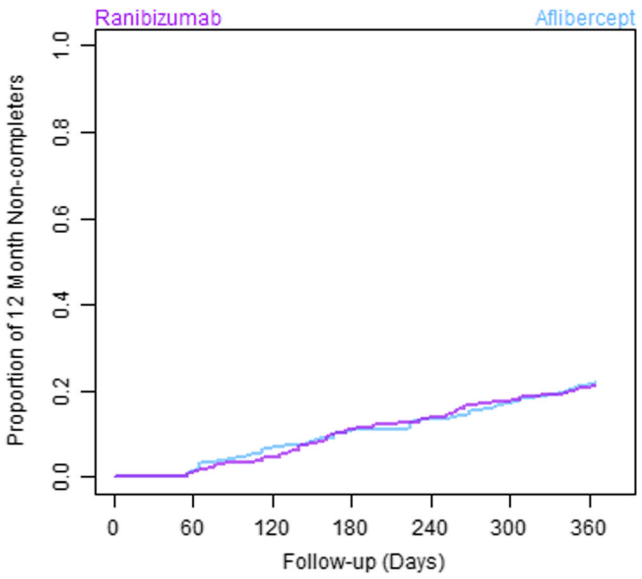

Fig. 6 Kaplan-Meier survival analysis of length of time to loss of follow-up for ranibizumab and aflibercept

with atrial fibrillation were started on warfarin in 2010, but by 2013, only 30% received warfarin as a first-line treatment, while the remaining 70% received newer anticoagulants that required less or no monitoring [23].

Following the approval of aflibercept to treat nAMD, physicians were offered an alternative to ranibizumab, which was the only approved drug until then. Apart from sales figures, no detailed pharmacoepidemiologic data are available on the use of both drugs in Australia to reflect whether physicians preferred one treatment over the other. Sales figures for VEGF inhibitors are difficult to interpret because both aflibercept and ranibizumab have also been approved for treating diabetic macular oedema and retinal vein occlusions.

The publication of outcomes of the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD studies (VIEW) RCT of aflibercept for nAMD [17] raised expectations that fewer doses of aflibercept might be required to treat nAMD. In a recent study from routine clinical practice in the USA, the mean [SD] numbers of injections received in the first year by patients treated with ranibizumab or aflibercept were not clinically different (4.9 [3.3] vs. 5.2 [2.9], respectively) [24]. There was no difference between injection frequency between ranibizumab and aflibercept in the present study (7.3 [2.4] vs. 7.2 [2.2], respectively). Although the pivotal RCTs showed that aflibercept was non-inferior to ranibizumab when used at two-monthly intervals (after initial three treatments at monthly intervals) compared with monthly ranibizumab, none of the practitioners studied appear to have adopted the recommended two monthly aflibercept treatment regimen after the initial three doses given at monthly intervals [7, 17]. The present analysis additionally found that as a whole, Australian clinicians generally use both drugs as first-line treatment equally often.

One notable finding was that patients receiving ranibizumab were significantly older than those receiving aflibercept (Fig. 1). This may be partially due to a publication of a paper in 2013 that suggested there may be a greater risk of stroke in patients over 85 years old with aflibercept based on an investigation by the European Authorities [25]. To date, RCTs have not had enough statistical power to detect uncommon potential side effects of anti-VEGF therapy such as stroke [26].

Although no information is available on why either of the drugs were chosen as initial treatment for an individual patient, lesion size may have also affected the choice of drug. Median lesion size of the aflibercept group was significantly larger than in the ranibizumab group (2450 vs. 2000 μm; $P = 0.008$; Table 1), otherwise there was no difference in the baseline characteristics of the two groups. Following the presentation of data from the VIEW trials on retinal pigment epithelial detachment (RPED) resolution using aflibercept [27], practitioners may have had a preference for aflibercept in such cases.

The hope that the newer drug, aflibercept, had a longer half-life and higher VEGF binding capacity is a possible reason that eyes were much more likely to switch from ranibizumab to aflibercept than vice versa. Since most clinicians administered three initial monthly injections, there were almost no switches directly after treatment initiation up to the first 120 days. The decreasing rate of switching over time may be evidence that physicians found no obvious benefit from this therapeutic manoeuvre while reports of the outcomes of switching from ranibizumab to aflibercept have been mixed. Experience in patients on long-term anti-VEGF treatment with ranibizumab that were switched to aflibercept and did not show marked increase in VA or relevant rate of CNV inactivation may have influenced decision-making towards less switching [28]. There are currently limited data on the outcomes of switching from aflibercept to ranibizumab. It is likely that persistent lesion activity or poor outcomes were the primary reasons for switching in the few cases where switching from aflibercept to ranibizumab was observed.

The similar rate of lost to follow-up in both groups was also observed in previous analysis. In our populations, reasons for discontinuation are often due to external circumstances, such as patients transferring their care to clinicians closer to home or death of the patient [29].

The present analysis has several strengths and limitations. Using the FRB! database allowed a detailed analysis of nAMD patients treated in routine clinical practice, both in private practice and academic centres, reflecting real-world utilisation of both anti-VEGF drugs for the treatment of nAMD. The reimbursement conditions and posology have been the same for ranibizumab and aflibercept since they were approved in Australia, so physicians were free to choose either drug for eyes with nAMD. Furthermore, treatment regimens such as pro re nata, monthly fixed dosing and treat-and-extend were at the discretion of the treating physician and was not recorded in the FRB! database, although most Australian practitioners employ a treat-and-extend regimen [30]. The large cohort of patients that we studied provided a robust analysis across multiple sites. While the quality of observational information may be variable, the FRB! registry includes quality assurance measures to ensure high-quality data [19]. The lack of information on the presence of RPEDs—which was not routinely collected—is a limitation as this may have influenced the choice of drugs.

These pharmacoepidemiologic data indicate that there seemed to be a slight preference for ranibizumab over aflibercept among Australian practitioners when treating patients with nAMD. Ranibizumab was used more often in older patients while aflibercept was used more often in patients with a greater lesion size.

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Compliance with ethical standards

Conflict of interest The authors state they have no conflicts of interest to declare. Mark Gillies is a Sydney Medical Foundation Fellow and is supported by an NHMRC practitioner fellowship. Daniel Barthelmes was supported by the Walter and Gertrud Siegenthaler Foundation Zurich, Switzerland and the Swiss National Foundation. Vincent Daien was supported by the research grant of the French Society of Ophthalmology.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study. For this type of study, formal consent is not required.

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