Intravitreal therapy in neovascular age-related macular degeneration—adapting to increasing demand and changing times

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ABSTRACT

AIMS: To report the outcomes of patients with neovascular age-related macular degeneration (nAMD) at Palmerston North Eye Clinic (PNEC) during 2020 and 2021, comparing time to treatment initiation based on nurse-injector availability and during COVID-19 restrictions.

METHODS: Data were recorded from a prospective database for patients with nAMD at PNEC. Each patient's electronic health record was reviewed to ensure the accuracy of the database and to fill in missing data points. Statistics were done using Microsoft Excel and R.

RESULTS: One hundred and fifty-six eyes were diagnosed with nAMD during the study. Mean time from referral triage to first injection was 13.08 days across the study period. Time to treatment initiation was not statistically different by level of COVID-19 restriction but there was a significant difference in first specialist appointment to injection interval when three nurse-injectors were available compared to four. The effect seemed most evident in subsequent months after reduced nurse-injector availability began.

CONCLUSIONS: Despite an increase in nAMD diagnoses each year, PNEC continues to meet national guidelines for interval from referral to treatment initiation through innovations in practice. As demand for intravitreal injections continues to increase, further resourcing and research into newer agents will be required to keep wait times compliant with guidelines.

Age-related macular degeneration (AMD) is the leading cause of visual impairment in older adults in developed countries, including New Zealand.[1,2] Neovascular AMD (nAMD) represents a subset of AMD that can cause rapid and irreversible vision loss if untreated due to macular neovascularisation and subsequent macular scarring.[1] Since their approval in the early 2000s, intravitreal injections of anti-vascular endothelial growth factor (VEGF) have become the mainstay of therapy for patients with nAMD.[3] These agents oppose the effects of VEGF and have been found to improve and stabilise vision in nAMD.[3] Patients typically complete an induction sequence of three injections spaced 4 weeks apart, followed by repeat injections at fixed intervals or by a "*pro re nata*" (PRN) or "treat and extend" protocol to sustain the benefits achieved during induction.[1] Commonly used anti-VEGF agents in Palmerston North Eye Clinic (PNEC) include bevacizumab (Avastin®) and aflibercept (Eylea®).

The ongoing need for anti-VEGF therapy following induction has caused a substantial increase in workload for ophthalmology services world-wide.[4] PNEC is no exception to this, with a previous audit demonstrating a 32.6% increase in injections for those diagnosed with nAMD between 2018 and 2019.[5] Despite this, PNEC has not had any increase in medical staff. The demand for intravitreal injections is expected to continue rising with the increasing prevalence of AMD due to the ageing population.[2] The MidCentral Region will likely be disproportionately affected as existing population data show that 18.9% of people are aged over 65 years in MidCentral compared to the national average of 16.5%.[6]

To cope with increasing demand for intravitreal injections, ophthalmology services began training senior nurses to deliver injections as this has been shown to be an effective and safe practice.[7] At PNEC, this role has been expanded to include nurse-led "hybrid clinics", where patients with stable nAMD receive an intravitreal injection from a nurse-injector and have optical coherence tomography (OCT) and fundus photographs taken on the same day. These are reviewed by extended-practice registered nurses to determine appropriate timing of the next injection according to a standard treat and extend protocol. By reducing the number of patients with stable nAMD requiring consultant ophthalmologist review, clinic time can be reallocated to first specialist appointments

(FSA), reducing waiting times for new referrals. A 2019 study at PNEC showed an average time of 14.3 days from referral triage to first injection.[5] This almost achieves the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) recommendation that patients with suspected nAMD are assessed within 1 week of referral and initiate treatment within 1 week following initial assessment.[8]

In recent years, the COVID-19 pandemic has posed major barriers to the delivery of healthcare services due to institutional policies to reduce the number of patients attending hospital, and self-imposed behaviours of the public to limit their exposure to the virus.[9] Many ophthalmology clinics reported fewer referrals and a rise in missed appointments during the pandemic.[9] This was expected to result in delayed treatment initiation and worse visual outcomes.[9]

The aim of this paper is to report the outcome of patients with nAMD at PNEC over the preceding 2 years. The primary outcome is the time from referral triage to first injection, to determine if PNEC is meeting the RANZCO guidelines. The time from triage referral to first injection will be compared by level of COVID-19 restriction and number of available nurse-injectors. Secondary outcomes include the change in visual acuity (VA), total number of intravitreal injections received and the final injection interval at 18 months from diagnosis.

Methods

In 2017, a prospective database of patients with nAMD was developed by PNEC. Details of each patient's treatment and visual outcomes are recorded in the database, either by a nurse or ophthalmologist, following each appointment. This study used the database to identify patients with a new diagnosis of nAMD in 2020 and 2021. Data on the number and type of intravitreal injections received, as well as VA at 6, 12 and 18 months after diagnosis, were collected. Ophthalmology clinic notes from each patient's electronic health record were reviewed to validate the accuracy of the data and identify the interval between referral triage, FSA and first intravitreal injection.

The study period of 2020 and 2021 was chosen as it reflects the period of peak disruption to healthcare services by COVID-19. The Mid-Central District Health Board (DHB) was under COVID-19 Level 3 and 4 restrictions between 23 March 2020–11 May 2020 and 17 August 2021–6 September 2021. Nurse-injector availability was as follows: Four injectors were available from January 2020 to September 2020 and from October 2021 until the end of the study period. There were three injectors between April 2021 and September 2021, two injectors between September 2020 and March 2021 and one injector in the month of March 2021.

Data are presented as proportions and summary counts. Statistical analysis utilised Microsoft Excel and R.[10,11] Comparison between groups utilised Mann–Whitney and Kruskal–Wallis tests. Confidence intervals (CI) were constructed using the Hodges–Lehmann estimator (HLE). P-values <0.05 were considered significant. Eyes from the same patient were treated independently during analysis. The triage to injection interval could not be determined in eight eyes due to an unknown referral triage date. Two eyes were referred for cataracts and one patient initially declined treatment, and so were not included in the analysis of triage to injection time. The FSA to injection interval was determined and is reported in all cases except for the patient who initially declined treatment. This study is a continuation of previously published work by Yap et al. and received locality approval from MidCentral DHB.[5]

Results

Patient characteristics

A total of 156 eyes from 135 unique patients were diagnosed with nAMD during the study period. Sixty-five eyes were diagnosed in 2020, compared with 91 eyes in 2021. The mean age in years at diagnosis in males was 80.3 (SD 8.2), in females was 80.6 (SD 7.9) and overall was 80.5 (SD 8.0). Other patient characteristics are reported in Table 1.

Injections and intervals

The mean time in days from referral triage to FSA (N=146) was 10.76 (SD 12.68) and from FSA to first injection (N=155) was 2.48 (SD 5.93), with 116 (74%) eyes receiving their first injection on the same day as FSA. The mean time in days from triage to first injection was 11.67 (SD 12.30) in 2020 (N=60) and 14.07 (SD 15.66) in 2021 (N=85), with an overall (N=145) mean of 13.08 (SD 14.37) across the study. Forty-eight (31%) eyes had an interval greater than 14 days between triage and first injection. The mean and median time from referral triage to first injection, and FSA to first injection by month of diagnosis, are displayed in

Table 1: Characteristics of patients diagnosed with nAMD at PNEC in 2020 and 2021 (N=135).

Characteristic	Number of patients, N/135 (%)
Sex	
Males	66 (49)
Females	69 (51)
Ethnicity	
NZ European	128 (95)
NZ Māori	2 (1)
Pacific	2 (1)
Other	3 (2)

Figure 1: Jitter plot with mean (blue) and median (yellow) time between referral triage and first intravitreal injection (N=145). The dashed line is at 14 days. The blue rectangles represent the timing of COVID-19 Level 3 and 4 restrictions affecting MidCentral DHB. The coloured bars indicate the number of nurse-injectors available at each time period.

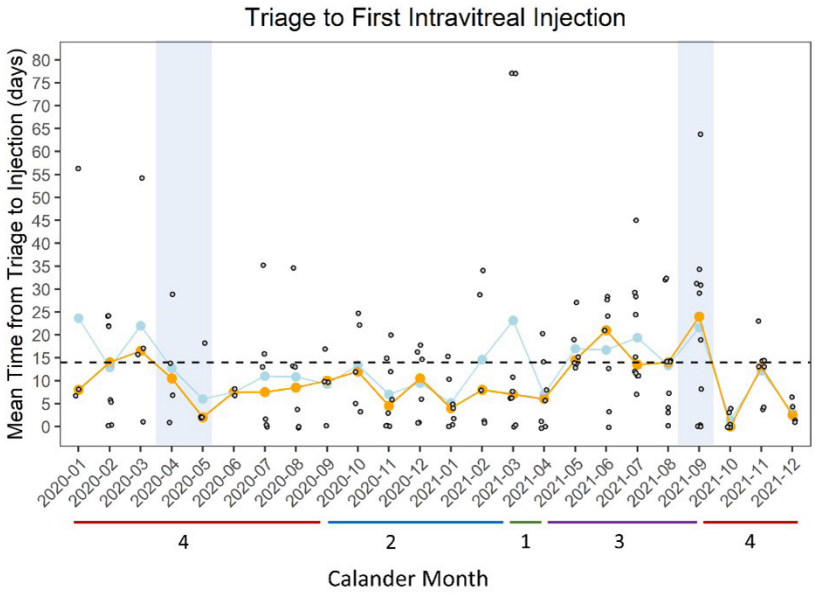

Figure 1 and 2 respectively.

The intervals from referral triage to first injection and FSA to first injection during and outside of COVID-19 restrictions are displayed in Table 2. There was no statistically significant difference in triage to first injection or FSA to first injection by level of COVID-19 restriction ($p>0.05$).

Table 3 displays the mean and median time from referral triage to first injection compared to the number of nurse-injectors. A statistically significant difference in FSA to injection interval by nurse-injector availability was noted ($p=0.005$). Further analysis with pairwise Mann–Whitney tests demonstrated this was due to a difference in FSA to injection time when three nurse-injectors were available compared to four ($p=0.0003$, HLE=$4.21e^{-5}$, 95% CI $6.69e^{-5}$–$2.57e^{-5}$).

Figure 2: Jitter plot with mean (blue) and median (yellow) time between FSA and first intravitreal injection (N=155). The blue rectangles represent the timing of COVID-19 Level 3 and 4 restrictions affecting MidCentral DHB. The coloured bars indicate the number of nurse-injectors available at each time period.

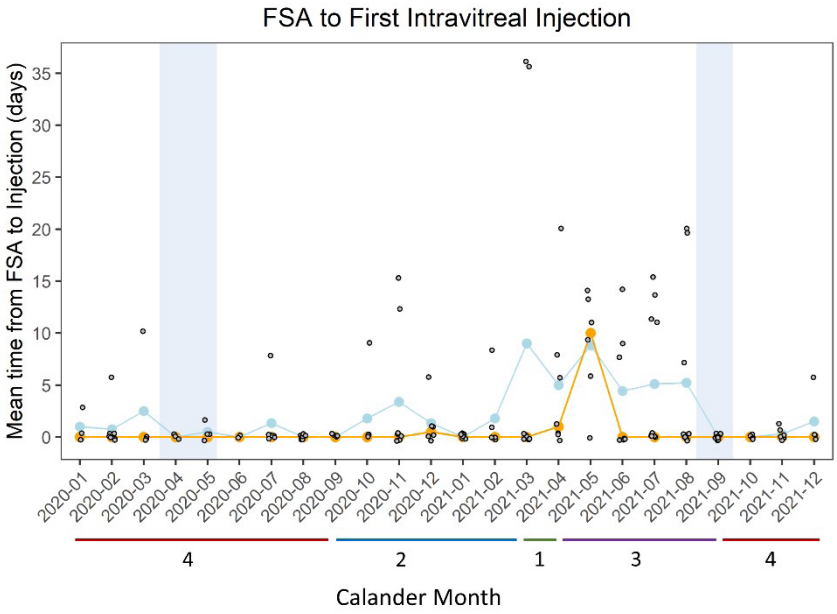

Table 2: Mean and median time in days from referral triage and FSA to first intravitreal injection during and outside of COVID-19 Level 3 and 4 restrictions.

Time period	N	Mean (SD)	Median	HLE	95% CI	P-value*
Referral triage to first injection						
During COVID-19 restrictions	6	13.33 (13.13)	10.5	4.84e-5	-9.0–13.0	0.86
Outside COVID-19 restrictions	139	13.06 (14.46)	10.0			
FSA to first injection						
During COVID-19 restrictions	6	0 (0)	0	0	-7.12e-5–0	0.15
Outside COVID-19 restrictions	149	2.58 (6.03)	0			

*P-value calculated by Mann–Whitney test.
FSA = first specialist appointment; HLE = Hoges-Lehmann estimate; CI = confidence interval, calculated by the Hodges-Lehmann estimator.

In 2020, 65 eyes were diagnosed with nAMD compared to 91 eyes in 2021. In the first 6 months of treatment, eyes diagnosed with nAMD in 2020 (N=65) received a total of 315 injections while those diagnosed in 2021 (N=91) received 419 injections. After 18 months, eyes diagnosed with nAMD in 2020 had received a total of 627 injections while those diagnosed in 2021 had received 876 injections. The mean final injection interval for eyes still receiving treatment after 18 months (N=111) was 8.8 (SD 4.1) weeks.

Following the 18-month treatment period, 111 eyes were still receiving injections. Of the 45 eyes not receiving treatment, 26 had end-stage disease, nine were in patients that declined ongoing treatment, six were in patients that had died, three were in patients lost to follow-up and one was treated with a PRN protocol and had a dry macula not requiring treatment.

Table 3: Mean and median time in days from referral triage and FSA to first injection based on the number of available nurse-injectors.

Number of available nurse-injectors	N	Mean (SD)	Median	P-value*
Referral triage to first injection				
1 Nurse-injector	8	23.13 (33.46)	7	0.06
2 Nurse-injectors	35	9.31 (9.12)	6	
3 Nurse-injectors	49	16.29 (13.32)	14	
4 Nurse-injectors	53	11.08 (12.81)	7	
FSA to first injection				
1 Nurse-injector	8	9.00 (16.66)	0	0.005
2 Nurse-injector	37	1.54 (3.66)	0	
3 Nurse-injector	50	4.36 (6.40)	0	
4 Nurse-injector	60	0.62 (1.97)	0	

*P-values calculated by the Kruskal–Wallis test.
FSA = first specialist appointment.

Table 4: Median VA in LogMAR across the study period based on triage to first injection interval.

Triage to injection	N	Initial VA median (IQR)	Final VA median (IQR)
Fewer than 14 days	88	0.61 (0.36)	0.54 (0.54)
14–28 days	39	0.60 (0.45)	0.60 (0.57)
More than 28 days	18	0.65 (0.47)	0.60 (0.65)

VA = visual acuity; IQR = interquartile range.

Table 5: Visual outcomes of patients diagnosed with nAMD in 2020 and 2021.

Outcome measure	2020, N/65 (%)	2021, N/91 (%)
Eyes with stabilisation or improvement in visual acuity	55 (85)	72 (79)
Eyes with improvement in visual acuity	8 (12)	22 (24)

During the study, 50 eyes switched from Avastin® to Eylea®. The mean number of injections before switching to Eylea® was 6.75 (SD 3.08). The mean final injection interval in weeks was 10.45 (SD 4.12) for those treated with Avastin® (N=66) and 6.26 (SD 2.57) for those treated with Eylea® (N=45).

Visual acuity

The median (IQR) initial and final VA based on triage to injection time is summarised in Table 4.

The number and percentage of eyes achieving stabilisation and improvement in VA is displayed in Table 5. At 18 months, 37 (24%) eyes met the monocular driving standard (N=156), with 66

(49%) patients meeting the binocular driving standard (N=135).

Discussion

Across the study period, we observed an increase in the number of eyes diagnosed with nAMD by 40% from 65 eyes in 2020 to 91 eyes in 2021, which is a continued increase compared to a previous PNEC study with 57 and 44 diagnoses of nAMD in 2018 and 2019 respectively.[5] The 50% increase in incidence between studies is consistent with the expected rise in cases with the ageing population.[2] Similarly, the number of administered injections increased by 39.7% from 627 in 2020 to 876 in 2021, which represents a substantial increase in the workload of PNEC. Despite the increased workload, PNEC achieved a mean time between triage and first injection of 13.08 days, which meets the RANZCO guideline of treatment initiation within 14 days.[8] This result compares favourably to findings in other healthcare systems, including the large National Ophthalmology Database (NOD) audit conducted in the United Kingdom in which only one-quarter of patients received treatment within 14 days of referral.[12]

Most patients were of NZ European ethnicity, with only two patients of NZ Māori ethnicity. This is lower than expected based on the Māori population size in Palmerston North but is consistent with the reported low prevalence of AMD in Māori and high prevalence in Europeans.[2,13] Barriers to accessing healthcare for Māori may also be implicated, though further studies would be required to assess this.

The increasing incidence of AMD has made it necessary to develop new strategies to keep wait times compliant with the RANZCO guidelines. This has been aided by the widespread adoption of the treat and extend protocol over the PRN protocol for intravitreal injections. The treat and extend protocol involves an injection at every visit, meaning the number of injections for each clinic is predictable and clinic resources can be prepared in a way the PRN protocol does not allow. PNEC's nurse-led hybrid clinics represent a unique integration of systems to streamline patient workflow by having imaging and injections on the same day, which extended-practice registered nurses review to determine subsequent treatment intervals by a treat and extend algorithm, with remote support available if needed. This allows more time for ophthalmologists to see new patients, reducing the time between referral triage and injection.

The majority of time between referral triage and first injection consisted of wait time for the FSA, as increasing numbers of patients received their first injection on the same day as their FSA by available nurse-injectors. Although there was no statistically significant relationship between triage to first injection and fewer nurse-injectors, there appeared to be a delayed effect in subsequent months that likely corresponded to the accumulation of patients created by the lack of same-day nurse-injector availability. The time from triage to injection returned within RANZCO guidelines once available nurse-injectors were sustained at an adequate level and the backlog was cleared. The increase in wait times appeared to disproportionately affect the time from FSA to first injection, with a statistically significant difference noted when three nurse-injectors were available compared to four, although the effect size appears to be small. This observation is likely because, in the absence of nurse-injectors, medical staff were unable to perform same-day injections during busy clinics. In addition to reducing wait times, nurse-injectors helped achieve other goals including fewer clinic visits for patients as injections are received during follow-up clinics, and less time for the administration components of organising clinics. This had the added environmental benefit of reducing patient travel-related carbon emissions, which is the largest contributor to emissions associated with intravitreal injections.[14] As the demand for intravitreal injections continues to increase, more resourcing will be important, particularly for injections and patient reviews at satellite clinics, helping to maintain acceptable wait times while also reducing inequity and travel-related emissions.

This study also assessed the impact of COVID-19 on triage to injection times. While there was no statistically significant difference, we observed a modest decrease in wait times during COVID-19 Level 3 and 4 restrictions compared to outside of these restrictions. This likely reflects PNEC's practice during COVID-19 Level 3 and 4 restrictions of deferring non-urgent and semi-urgent appointments to accommodate FSA for those with urgent or sight-threatening conditions, including suspected nAMD, to facilitate prompt treatment, which is important considering the morbidity associated with undiagnosed and untreated nAMD.[1] However, there were only six diagnoses of nAMD during COVID-19 restrictions, which may reflect a reduction in referrals from optometrists and general practitioners from the effect of COVID-19 on their practice, which would

be consistent with other ophthalmology services that reported a reduction in the number of referrals for nAMD.[9]

The median initial VA in LogMAR was similar regardless of triage to injection interval, although eyes with a shorter interval had the most improvement and best VA at the end of the study period. The percentage of eyes achieving an improvement in VA increased from 12% in 2020 to 24% in 2021. These are comparable figures to a previous PNEC study that demonstrated an improved VA in 10.5% and 31.8% of patients in 2018 and 2019 respectively.[5] The treatment of nAMD has not significantly changed during these periods, therefore we would not expect significant variability in outcomes—but, considering the increased demand for treatment, it is promising to see comparable outcomes to previous studies. We also observed stability of VA in 85% of eyes in 2020 and 79% of eyes in 2021 compared to the previous PNEC study that reported stability in 82.5% and 93.2% in 2018 and 2019 respectively.[5] These results are also comparable to the aforementioned NOD audit, suggesting PNEC is achieving similar visual outcomes to other developed countries.[12]

About half of patients maintained binocular VA meeting the NZ driving standard, which is slightly lower than the previous PNEC study that reported 58.3% and 62.5% of patients meeting the driving standard in 2018 and 2019 respectively.[5] This compares to the NOD audit that reported 40% of patients meeting the driving standard after 1 year.[12] Maintenance of driving standard vision is particularly important for the quality of life and independence of older adults, making it an important measure of vision to report.[15]

Eyes treated with Eylea® had a shorter interval between injections compared to those treated with Avastin®, despite the results of previous literature including the VIEW trial, which demonstrated non-inferior outcomes with Eylea® at larger intervals compared to the anti-VEGF agent ranibizumab—an agent demonstrated to be similar to Avastin®.[16,17] Our finding likely reflects more severe nAMD in those treated with Eylea® since eligibility criteria restrict its use to eyes with resistance to Avastin® following the induction series, and those that also have no structural damage to the fovea, among other criteria.[18] If access criteria to Eylea® were less restrictive, longer treatment intervals would likely be achieved. A newer intravitreal agent, faricimab, inhibits VEGF in addition to angiopoietin-2, another important molecule in angiogenesis and the pathogenesis of nAMD.[19] Faricimab has been shown to yield comparable outcomes at 12- and 16-week injection intervals compared to 4-weekly injections of ranibizumab.[20] Faricimab is not yet available in New Zealand, but, if introduced, may enable longer treatment intervals to be achieved. This could help alleviate the burden of frequent injections on patients and ophthalmology clinics and in turn improve wait times between referrals and treatment initiation.

The PNEC prospective database of individuals with nAMD is a useful tool to audit clinical practice and patient outcomes, but there is variability in the completeness of data since it relies on manual input. The lack of automation in data entry and the busy clinical environment meant it was necessary for each patient's electronic health record to be reviewed to fill in missing data points and ensure the quality of the data already within the database.

Another limitation of this study is the sample size in each of the groups being compared. Only six eyes were diagnosed with nAMD during COVID-19 restrictions, limiting the ability of our study to detect a statistically significant difference if one exists. This limitation also occurred when comparing intervals by nurse-injector availability as each subgroup has a reduced number of eyes.

This study is also limited by the definition of improvement and stability in VA. An improvement in VA is defined as an increase of 15 letters, while stability is defined as a loss of fewer than 15 letters.[21] This becomes a limitation at the extremes of VA, since those with good VA do not have a significant scope to improve their VA further, while those with poor VA are unable to lose 15 letters simply because of their starting acuity. These phenomena are termed the ceiling and floor effect respectively and are observed in other studies using these definitions.[21] We have reported the median for VA data to give a fairer representation of VA since it is less affected by eyes with extremes of VA.

The increasing demand for intravitreal injections to treat nAMD represents a significant increase in workload for ophthalmology services. The introduction of nurse-led injections and extended-practice nurse hybrid clinics has been instrumental in managing this demand at PNEC, especially considering the absence of increased funding for recruitment of ophthalmologists. As research into anti-VEGF and other agents increases, longer injection intervals may be achievable, which will help keep services compliant with RANZCO guidelines while reducing the treatment burden for patients and ophthalmology clinics.

COMPETING INTERESTS
Nil.

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