Graefes Arch Clin Exp Ophthalmol
DOI 10.1007/s00417-014-2885-y

RETINAL DISORDERS

Rate of vision loss in neovascular age-related macular degeneration explored

Juan P. Real · Gladys E. Granero · Mariana O. De Santis · Claudio P. Juarez · Santiago D. Palma · Simon P. Kelly · José D. Luna

Received: 13 August 2014 / Revised: 17 November 2014 / Accepted: 22 November 2014

Abstract
Purpose To explore decline in visual acuity in patients with neovascular age-related macular degeneration (n-AMD) awaiting intravitreal bevacizumab or ranibizumab treatment following initial diagnosis and after disease reactivation.
Methods Retrospective analysis of 74 treatment-naïve patients (84 eyes) in two centers in Córdoba, Argentina. The time between treatment indication and intravitreal injection, and the changes in BCVA produced during this delay were studied in both periods. A linear regression model to search the impact of time on progression visual impairment was conducted.
Results In both periods, a significant reduction in vision occurred awaiting intravitreal injection. The longer the delay, the greater the vision loss (R2=0.55 $p<0.01$) and the less improvement following treatment (Pearson coefficient −0.26). The result of the model shows that the change in vision as a function of initial delay were best described by a polynomic model with a mean loss of 5 letters in the first 3 weeks, a slowdown in the rate of change of VA, and a dependence of visual acuity at the moment of diagnosis . The loss of visual acuity after reactivation shows the same behavior as at the onset of the disease but independent of visual acuity prior to reactivation.
Conclusion Visual loss awaiting injection intravitreal anti-VEGF is clinically significant and with an asymptotic pattern, with early rapid loss of vision in both the onset of the disease and the reactivation. Initiation of anti-VEGF treatment must be undertaken urgently, as should retreatment of disease activation to reduce visual loss.

Keywords Age-related macular degeneration · Bevacizumab · Disease progression · Health systems · Patient safety · Ranibizumab

Introduction

Age-related macular degeneration (AMD) is the leading cause of severe visual loss in the developed world. The incidence and prevalence of AMD are increasing as the population ages and life expectancy improves. The recent development of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has presented a major breakthrough in the care of patients with wet or neovascular-AMD (n-AMD). Since the introduction of such medications, maintenance or improvement of vision is now an expectation. It is gratifying that blindness rates from AMD are reducing significantly at population levels in developed economies since such treatments became available [1–3]. A dosing regimen of three injections followed by pro-re-nata (PRN) treatment is frequently undertaken in 'real world' care, and such dosing is recommended in some clinical practice guidelines [4–6] and based in part on the PrONTO study protocol [7]. Re-treatment criteria include: loss of ≥5 letters on a standardized visual acuity chart or increase in central retinal thickness, or the detection of any fluid on optical coherence tomography

J. P. Real · G. E. Granero · S. D. Palma
Pharmacy Department of the Faculty of Chemical Sciences, National University of Córdoba UNITEFA (CONICET), Cordoba, Argentina

C. P. Juarez · J. D. Luna (✉)
Vitreo-Retinal Department, Centro Privado de Ojos Romagosa SA - Fundación VER, Córdoba, Argentina Dean Funes, 432, 5000 Córdoba, Argentina
e-mail: moonpintojd@outlook.com

M. O. De Santis
Institute of Economics and Finance, School of Economics Sciences, National University of Córdoba, Córdoba, Argentina

S. P. Kelly
Ophthalmology Department, Royal Bolton Hospital, Bolton, UK

Published online: 11 December 2014

(OCT) imaging 1 month after an injection. All such criteria are based on changes from the previous evaluation. Disease reactivation or recurrence is considered to have occurred when such changes are present at follow-up clinical visit.

Recent studies have demonstrated that PRN treatment with either ranibizumab or bevacizumab undertaken with monthly monitoring and immediate retreatment following disease recurrence are of broadly similar ophthalmic efficacy [8, 9]. Monthly visits may be problematic for patients, payers, and physicians. Thus some ophthalmologists adopt flexible regimes, such as treat and extend, and may lengthen the period between follow-up examinations when disease is stable. It is of relevance that patients may experience delay in access for n-AMD care in some health systems for whatever clinical or non-clinical reasons. Delays may include delay in obtaining initial anti-VEGF dosing, and delay in acquiring an injection appointment visit following disease recurrence. In a review of patient safety incidents (PSI) related to anti-VEGF medication use, reported to the National Patient Safety Agency, delay in treatment or assessment was the principal PSI reported in England and Wales [10]. Such matters pose a universal patient safety concern, and are clinically relevant in all health economies.

Understanding of the natural history of visual acuity decline in untreated n-AMD patients in the anti-VEGF era is limited. Muether et al. [11] assessed the temporal relationships of changes in vision in both the initiation stage and at the stage of reactivation, and found greater loss of vision in the latter period. However, the delay time (6 to 58 days) and loss of visual acuity (VA) after reactivation (only two patients lost more than 1 line) were too small to describe the phenomenon in a manner equivalent to the initial phase.

As we have previously described, n-AMD patients in Argentina must overcome several bureaucratic barriers to access anti-VEGF treatment [12]. In Argentina, bevacizumab is not covered by health insurance and ranibizumab is. However, funding approval for ranibizumab is often delayed to verify the clinical indication. On average, a delay of 160 days occurs. This same situation occurs for subsequent retreatment. The fact that this delay in access to initial treatment and retreatment is so prolonged provides a unique setting to study the natural rate of progression of untreated n-AMD and with OCT imaging.

The present study assesses the impact of delay on distance visual acuity (VA) in such patients while awaiting first anti-VEGF injection, and again following subsequent disease recurrence and awaiting retreatment injections.

Methods

We undertook a retrospective analysis of all consecutive charts and imaging studies of patients with n-AMD treated for the first time with intravitreal ranibizumab or bevacizumab at two of the major ophthalmological centers of Córdoba, Argentina (Centro Privado de Ojos Romagosa and Ophthalmology Department, Catholic University of Córdoba) from January 2007 to December 2012. During that time, there were delays in care of n-AMD patients in Argentina due to administrative issues.

This study complied with the Helsinki Declaration, and was approved by the Institutional Ethics Committee of the National Clinical Hospital. To be included in the study, patients: (1) had to be at least 50 years old, (2) had to have a best-corrected visual acuity (BCVA) of 20/40 to 20/320 and diagnosis of n-AMD, as confirmed by fundus fluorescein angiogram (FFA) and spectral-domain optical coherence tomography (SD-OCT), and (3) had to have been treated by usual care in one of the above centers. Charts of patients in whom laser photocoagulation treatment, verteporfin photodynamic therapy (PDT), or prior intravitreal therapy had been undertaken were excluded from the analysis, as well as those who during the monitoring year received a combined treatment with other intravitreal drugs and/or surgical treatments in the study eye, such as cataract surgery

Information gathered at baseline visit included: (1) age and gender at presentation, (2) time elapsed from the first ophthalmological consultation with macular visual symptoms and date of therapy initiation (waiting time), (3) intraOCT and FFA findings, (4) BCVA, (5) presence or absence of cataracts, and (6) type of CNV. Best-corrected Snellen visual acuity was recorded and converted to logarithm of minimum angle of resolution (logMAR) units. Re-treatment criteria were as the PrONTO study protocol [7].

Unresponsive patients — those with BCVA below 20/320 after three intravitreal injections (loading phase) — were excluded from analysis. Patients without delay — those treated within 4 calendar days of disease re-activity — were also excluded. Delay after reactivation is the time in days between diagnosis of reactivation and intravitreal injection.

A linear regression model exploring impact of delay on decline of vision was conducted. The dependent variable was the visual acuity (VA) change, expressed in ETDRS letters. Delay in days, patient age and gender, and anti-VEGF medication agent were the independent variables. The model can be expressed as follows:

$$VAchange_i = \sum_{1}^{K} \alpha_k delay_i^k + \beta_1 gender_i + \beta_2 age_i + \beta_3 drug_i + \beta_4 VAdx_i \varepsilon_i \quad (1)$$

Where $VA\ change_i$ is the VA change in letters in the treated eye (i) between diagnosis and treatment, $delay_i$ is the time in days between diagnosis and intravitreal injection in the treated

eye, $gender_i$ is the gender of the patient, age_i is patient age at the time of diagnosis, $drug_i$ is the anti-VEGF medication drug (ranibizumab or bevacizumab) injected to the treated eye, and $VAdx$i is the visual acuity of the eye at time of diagnosis. α_k and β_1 to β_3 are the coefficients associated to the respective variables and ε_i is the error term of the model with a distribution $N(0, \sigma^2)$. Note that successive powers of the variable delay were included in the model in order to prove if the VA change presents a linear relationship with the delay or if a deceleration is observed as the delay increases. Moreover, the constant term was excluded from the model in the case that the change of VA is equal to 0 when the delay was 0.

The model described was estimated using data from both the patient data of the period before anti-VEGF treatment, and from patient data following subsequent disease reactivation after three loading doses of anti-VEGF medication. It is important to highlight that the delay period is defined as time between diagnosis of n-AMD by an ophthalmologist and time of first intravitreal injection or reinjection. Any period of known or unknown time between disease onset — as might be deduced from patient history — before confirmation of diagnosis by an ophthalmologist was not considered in this analysis.

All statistical analyses were performed using STATA 11.1 (StataCorp). Absolute and relative frequencies were used for qualitative variables, with means and standard deviations (SD) being used to summarize quantitative data. The normal distribution of data was tested using the Shapiro–Wilk test. Quantitative variables were compared using a Student's test for unpaired samples and a non-parametric Wilcoxon Mann–Whitney test if the variables did not meet the normality criteria. For comparisons of proportions, a Fisher–Irwin Test was used. The statistical relationship between the variables was analyzed by means of the Pearson's correlation test. A p-value of 0.05 or less was considered to be statistically significant.

Results

Eighty-four eyes of 76 patients met the inclusion and exclusion criteria. The mean age was 76.6 years (range, 51–93 years; SD, 8.07 years), and 55 patients were female (65 %). Predominantly occult CNV was recorded in 37 eyes (44 %), predominantly classic CNV in 28 eyes (33 %), and in 19 eyes (23 %) the CNV subtype was not recorded. 48 eyes (43 patients) were treated with bevacizumab, and 36 eyes (33 patients) with ranibizumab. The mean follow-up period was 1.81 years (range, 0.5–5.7 years).

Initial waiting time and its impact on treatment effectiveness

The mean duration of the waiting time from baseline visit to initial treatment was 87.5 days (median 60 days, range, 0–312 days; SD, 78.3 days). Patients lost an average of 10.67± 12.19 letters ($p < 0.01$) in this period. Patients gained 8.81 letters (SD 10.29) following three loading injections. An indirect correlation between change in vision following the loading phase and the waiting time was found; the longer the delay in time from diagnosis to treatment, the less likely was VA gain after treatment (Pearson coefficient −0.26, $p < 0.02$). Figure 1 and Table 1 show the mean change in the visual acuity and baseline characteristics of 84 eyes by waiting time percentiles.

After the end of the loading phase, 70 of 84 eyes had BCVA better than 20/320. Of these eyes, 40 had a diagnosis of recurrence, but 13 did not have a delay in access to the reactivation. Therefore, 27 had loss of vision compatible with this diagnosis and delay. The average time between the confirmation of disease recurrence and the time of retreatment (or time of the medical decision about the discontinuation of treatment) was 224 days (SD 190 days), which resulted in an average loss of 22.75±12.88 letters.

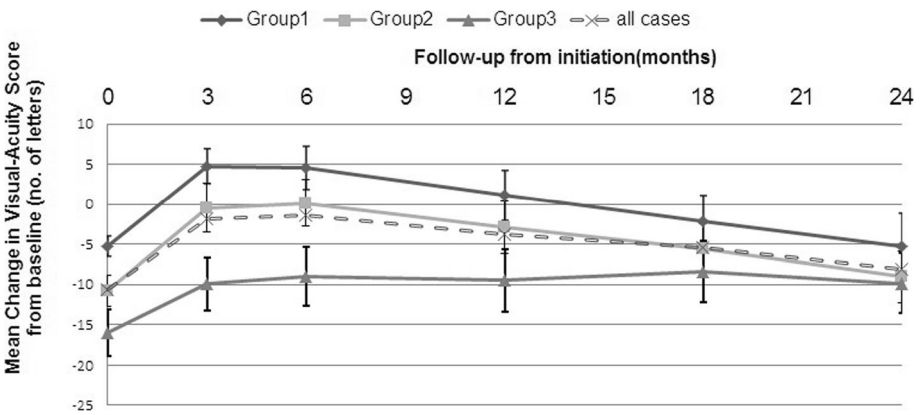

Fig. 1 Mean change in visual acuity letter scores from baseline to month 24 of follow-up. During waiting time (WT), all groups showed a statistically significant reduction in BCVA, being significantly higher in group 3. After loading phase, there was a significant visual acuity improvement in all groups, but the increase in group 3 was significantly lower than in the other two groups. After the end of the loading phase, all groups, but principally groups 1 and 2, showed a drop in visual acuity

Table 1 Comparison of baseline characteristics between time-delay-percentile groups

Baseline characteristics	Group 1	Group 2	Group 3
Number of cases	28	28	28
Female, *n* (%)	20 (71 %)	16 (57 %)	19 (68 %)
Age mean (SD)	74.54 (9.26)#	75.5 (7.65)	79.39 (6.56)#
Occult CNV lesion *n* (%)	13 (46 %)	12 (43 %)	12 (43 %)
Classic CNV lesion *n* (%)	10 (36 %)	6 (21 %)	12 (43 %)
Unknown/not stated of CNV lesion *n* (%)	5 (18 %)	10 (36 %)	4 (14 %)
VA > 20/40 *n* (%)	6 (21 %)	5 (18 %)	4 (14 %)
20/40>VA > 20/160, *n* (%)	18 (64 %)	18 (64 %)	14 (50 %)
20/200>VA > 20/320, *n* (%)	4 (14 %)	5 (18 %)	10 (36 %)
Mean VA all cases (LogMAR)	0.59 (0.28)	0.62 (0.28)	0.70 (0.31)
Pseudophakic cases	8 (29 %)	13 (46 %)	10 (36 %)
Bevacizumab	26 (93 %)+	21 (75 %)	1 (4 %)
Ranibizumab	2 (7 %)	7 (25 %)	27 (96 %)
Delay time	19.25 (10.47)*#	62.64 (18.55)**#	180.54 (62.8)**#

CNV choroidal neovascularization, *SD* standard deviation, *VA* visual acuity. *Delay time*: time between the diagnosis and the first intravitreal medication injection. # significant difference between group 1 and group 3. * significant difference between group 1 and group 2. + one patient was treated with bevacizumab in the loading phase and after that was treated with ranibizumab.

Group 1: patient with delay time<36 days (33.3 percentile); group 2: patient with delay time between 36 and 92 days (33.3 and 66.6 percentile); group 3: patients with delay time>92 days (66.6 percentile)

Temporal relationship of changes in visual acuity (VA)

The results of applying the regression analysis model (Eq. 1), linking the variability in the change in the VA with estimated time from the period before treatment, are shown in Table 2a.

The variables gender, age, and medication type were not statistically significant, and were excluded from the model. The variable 'delay' was statistically significant, and the effect of such delay on VA change was found to be non-linear. The adjusted determination coefficient (R2 adjusted) indicated that

Table 2 Regression model for change in visual acuity

A: Initial phase prior to first anti-VEGF injection. All variables are included

Variable	Parameter estimate	Standard error	*P* -value
AVdx	9.176438	4.316455	0.037
Delay	−0.4891728	−0.2255352	0.033
$Delay^2$	0.0071017	0.003618	0.053
$Delay^3$	−0.0000386	−0.0000196	0.052
$Delay^4$	6.59E−08	3.34E−08	0.052
Age	−0.0494113	0.0682915	0.472
Gender	−2.240315	2.605684	0.393
Medication	−3.653334	4.151343	0.382
Adj R-squared of model=0.57		F (8.76)=14.64	

B: Initial and reactivation periods when only delay-variables are included

	Intial period model	*P* -value	Reactivation period model	*P* -value
Delay	−0.446 (0.105)	<0.0001	−0.275 (0.06)	<0.0001
$Delay^2$	0.0063 (0.002)	0.004	0.00128 (0.0005)	0.014
$Delay^3$	−3.54E−05 (1.29E−05)	0.007	−2.76E−06 (1.12E−06)	0.022
$Delay^4$	6.25E−08 (2.36E−08)	0.01	1.9E−09 (7.76E−10)	0.023
Adj R-squared	0..5564		0.8925	
N	84		27	

AVdx: The best-corrected visual acuity at the moment of diagnosis. *Delay*: time between the diagnosis and the first intravitreal medication injection. Successive powers of the variable delay ($delay^2$, $delay^3$, $delay^4$) were included in the model in order to prove if the VA change presents a linear relationship with the delay or if a deceleration is observed as the delay increases

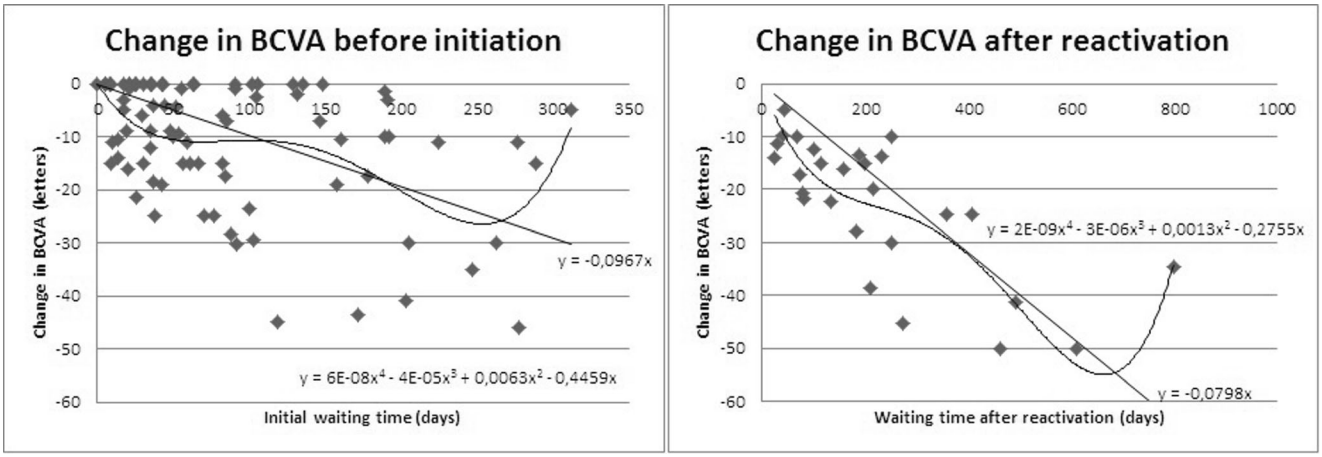

Fig. 2 *Left*: Scatterplot of change in VA from diagnosis and time between initial diagnosis and initiation of treatment (initial waiting-time). *Right*: Scatterplot of change in BCVA from diagnosis of reactivation and time between diagnosis of reactivation and subsequent intravitreal injection re-treatment (waiting-time after reactivation). Linear and polynomial regression analysis are illustrated in both images. *BCVA*=best-corrected visual acuity

57 % of the variability of the VA change is explained by the variables in the model. The linear regression model was also undertaken with data from eyes in the reactivation period. In the reactivation phase, the baseline vision at diagnosis (VAdx) did not correlate with outcome (p=0.46). It was only subsequent delay that was relevant to explain the variability of the VA change.

The R2 adjusted of Eq.1 in the reactivation period is higher than the respective coefficient in the initial phase (Table 2b). This result may be attributed to the fact that the variable 'delay' in the reactivation phase reflects with better precision the real delay between start of the reactivation process and repeated drug administration, since patients visit or should visit the ophthalmologist for regular monitoring.

A likelihood ratio (LR) test was conducted to examine if the polynomic model is statistically different from the linear model. The LR observed for the model estimated with eyes in initial phase was 14.84 with 3° of freedom, and the one for the reactivation phase was 20.67 with 2° of freedom, which thus rejects the hypothesis of the linear model being similar to the full model. In other words, the coefficients associated to the variable delay raised from the power 2 to 4 are relevant to explain the variability of the VA change. As it can be observed in Fig. 2, the impact of the delay on the VA was underestimated with the linear model, especially in early times.

Discusion

Early treatment of n-AMD is critical to achieve best clinical outcomes. We provide correlation between delay to both initial anti-VEGF treatment and retreatment (associated with administrative decisions and/or reasons intrinsic to the patient) with deterioration of vision over time. We found a non-linear decline in such vision loss. There is an initial rapid loss of vision in the early period of disease, followed by a slowing in the velocity of visual loss. The polynomial equations obtained in this study predict a loss of one logMAR line (5 letters) in less than 3 weeks. In contrast, Muether et al. [11] and Wong

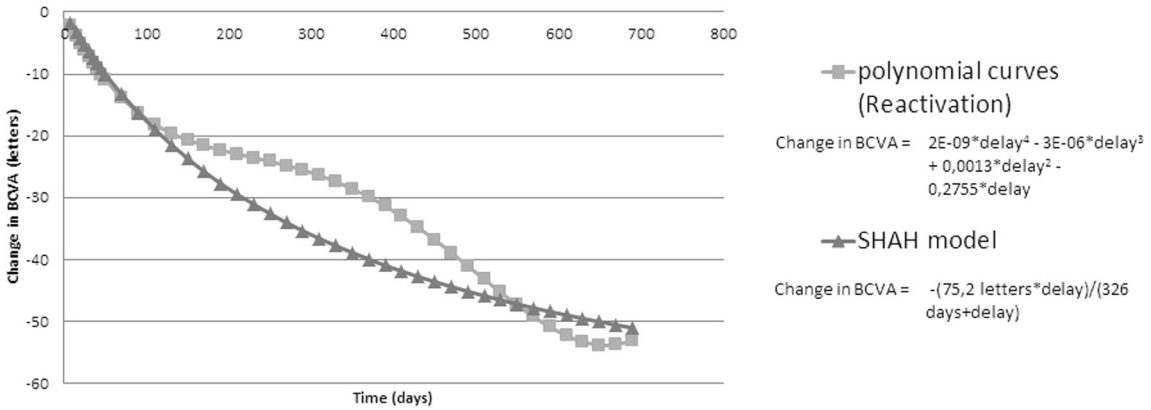

Fig. 3 Change in VA predicted by the polynomial function in the reactivation phase and by the Shah equation in the initial phase. *BCVA*=best-corrected visual acuity. *Delay*: time between the diagnosis and intravitreal injection

et al. [13] both reported such decline at 3 months. As shown in Fig. 2, we found the predicted values for the first-order equation underestimate the effect.

Shah et al. hypothesized that there is a uniform pattern of visual acuity decline among untreated AMD patients, and the apparent differences in the behavior of the untreated eyes in clinical trials arise from the differences in time of entry to such studies [14]. Shah et al. proposed a mathematical equation that initial VA is a major predictor of the behavior of subsequent vision as a function of time [14]. The clinical findings in our patients are compared with the theoretical model of Shah et al. (Fig. 3). We found the change in VA predicted by the polynomial function in the reactivation phase is similar to the change predicted by Shah's equation, and primarily in the early period of the natural history of n-AMD. The present study provides clinical validation for Shah's hypothesis, and it demonstrated that the loss of visual acuity after reactivation shows the same behavior as at the onset of the disease, but independent of visual acuity prior to reactivation.

We observed that prolonged waiting for intravitreal treatment had a major adverse impact on the recovery of vision after the loading phase. Other authors have shown that the vision that is lost after reactivation is rarely recovered fully following treatment with anti-VEGF agents, and the regain of lost vision is significantly higher when loss in VA had developed within the last month [15]. Thus, it is critical that ophthalmologists and health economies strive to shorten the time to initial treatment and retreatment for anti-VEGF medications if visual gain is to be achieved in real-world care for n-AMD patients

The rate of vision loss that occurs in the early period after disease reactivation highlights the clinical need to closely revaluate/monitor patients to ensure rapid diagnosis of and immediate treatment of reactivation. Frequent monitoring, which includes OCT imaging and prompt retreatment, are needed to avoid poor outcomes which have observed in clinical real-world care. [11, 13, 16].

The limitations of this study include our small patient numbers and the fact that only distance VA was recorded. There are other dimensions of vision function, such as contrast sensitivity, near acuity, reading speed, and patient reported outcomes which were not studied. Furthermore, OCT imaging was not carried out in all patients.

In conclusion, knowledge of the changes in vision at the time of presentation of n-AMD and following the loading period with intravitreal anti-VEGF are clinically important issues. Payers for healthcare and ophthalmologists need to be aware of the speed of vision loss in patients with n-AMD in both the initial phase and the reactivation of the disease. As n-AMD is a time-critical disorder, every day that treatment is delayed counts, whether by delay in diagnosis or impediment in access to intravitreal medication.

Considerable service improvements to facilitate swift access to anti-VEGF have been suggested [17–19]. Delays in access to initial treatment and or re-treatment may result in significant vision loss, and thus may negate much of the therapeutic response to anti-VEGF dosing. This is a matter of potential medico-legal and health economics significance. Prompt detection of active n-AMD at disease onset and following reactivation should be considered a critical practice point or red flag for ophthalmic systems of care. Once either matter is detected, treatment with intravitreal anti-VEGF should be considered as a matter of clinical urgency.

Acknowledgments The authors are grateful to Centro Privado de Ojos Romagosa SA-Fundación VER and University Clinic Reina Fabiola for their assistance. All authors participated in the development and writing of this manuscript and are fully responsible for this study.

Declarations SPK declares attending advisory boards of Bayer and Novartis and conference travel from Alcon, Bayer, and Novartis and lecture fees from Novartis. The authors declare no conflict of interest.

Funding statement This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Cackett P, Borooah S, Gavin M, Oladiwura D, Jeganathan VS, Scotland AMD, study group (2013) Intravitreal ranibizumab treatment of wet macular degeneration in SE Scotland — effect on blindness rates and 5 year follow up data. Invest Ophthalmol Vis Sci 54:372
2. Bloch SB, Larsen M, Munch IC (2012) Incidence of legal blindness from age-related macular degeneration in Denmark: year 2000 to 2010. Am J Ophthalmol 153:209–213
3. Skaat A, Chetrit A, Belkin M, Kinori M, Kalter-Leibovici O (2012) Time trends in the incidence and causes of blindness in Israel. Am J Ophthalmol 153:214–221
4. Ministry of Health, Madrid Health Service (2012) Criteria for use of bevacizumab and ranibizumab in patients with macular degeneration exudative [Internet]. Available at http://www.madrid.org/cs/Satellite?c=CM_Publicaciones_FA&cid=1354184974959&idConsejeria=1109266187266&idListConsj=1109265444710&idOrganismo=1142439317794&language=es&pagename=ComunidadMadrid%2FEstructura&sm=1109266101003. last accessed: July 2014
5. Ruiz-Moreno JM, Arias-Barquet L, Armadá-Maresca F et al (2009) Sociedad Española de Retina y Vítreo. [Guidelines of clinical practice of the SERV: treatment of exudative age-related macular degeneration]. Arch Soc Esp Oftalmol 84(7):333–344
6. The Royal College of Ophthalmologists (2013) Age-related macular degeneration: guidelines for management. Available at http://www.rcophth.ac.uk/; last accessed: July 2014
7. Fung AE, Lalwani GA, Rosenfeld PJ et al (2007) An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol 143(4):566–583
8. CATT Research Group, Martin DF, Maguire MG, Fine SL et al (2012) Ranibizumab and bevacizumab for treatment of neovascular

age-related macular degeneration: two-year results. Ophthalmology 119(7):1388–1398
9. IVAN study investigators, Chakravarthy U, Harding SP, Rogers CA et al (2013) Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. Lancet 382(9900):1258–1267
10. Kelly SP, Barua A (2011) A review of safety incidents in England and Wales for vascular endothelial growth factor inhibitor medications. Eye 25(6):710–716
11. Muether PS, Hermann MM, Koch K et al (2011) Delay between medical indication to anti-VEGF treatment in age-related macular degeneration can result in a loss of visual acuity. Graefes Arch Clin Exp Ophthalmol 249(5):633–637
12. Real JP, Luna JD, Urrets-Zavalia JA et al (2013) Accessibility as a conditioning factor in treatment for exudative age-related macular degeneration. Eur J Ophthalmol 23(6):857–864
13. Wong TY, Chakravarthy U, Klein R et al (2008) The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and metaanalysis. Ophthalmology 115:116–126
14. Shah AR, Del Priore LV (2007) Progressive visual loss in subfoveal exudation in age-related macular degeneration: a meta-analysis using Lineweaver-Burke plots. Am J Ophthalmol 143(1):83–89
15. Gerding H, Loukopoulos V, Riese J, Hefner L, Timmermann M (2011) Results of flexible ranibizumab treatment in age-related macular degeneration and search for parameters with impact on outcome. Graefes Arch Clin Exp Ophthalmol 249(5):653–662
16. Rakic JM, Leys A, Brié H et al (2013) Real-world variability in ranibizumab treatment and associated clinical, quality of life, and safety outcomes over 24 months in patients with neovascular age-related macular degeneration: the HELIOS study. Clin Ophthalmol 7: 1849–1858
17. American Academy of Ophthalmology Retina Panel (2008) Preferred practice pattern guidelines. Age-related macular degeneration. Available at http://www.aao.org/ppp; last accessed: July 2014
18. The International Council of Ophthalmology (2011) Age-related macular degeneration (Management recommendations). Available at http://www.icoph.org/resources/resources_detail/72/ICO-International-Clinical-Guideline-Age-Related-Macular-Degeneration-Management-recommendations-.html; last accessed: July 2014
19. Amoaku W, Blakeney S, Freeman M, Gale R, Johnston R, Kelly SP, McLaughlan B, Sahu D, Varma D, Action on AMD Group (2012) Optimising patient management: act now to ensure current and continual delivery of best possible patient care. Eye 26:S2–S21