Graefe's Archive for Clinical and Experimental Ophthalmology
https://doi.org/10.1007/s00417-020-04667-y

RETINAL DISORDERS

Outcome of treatment for neovascular age-related macular degeneration by practice-based ophthalmologists compared with a macula clinic

Cagdas Kaya[1] · Isabel B. Pfister[1,2] · Christin Gerhardt[1,2] · Justus G. Garweg[2,3]

Received: 7 November 2019 / Revised: 21 March 2020 / Accepted: 27 March 2020

Abstract

Purpose The aim of this study was to compare neovascular age-related macular degeneration (nAMD) treatment outcomes between ophthalmological practices and a specialized macula clinic.

Methods In this case series, we included 347 treatment-naïve eyes with nAMD (332 patients). All patients received intravitreal anti-VEGF treatment using ranibizumab or aflibercept at the discretion of the treating physician using a treat-and-extend protocol either by one of 28 practice-based ophthalmologists (group 1; $n = 215$ eyes) or at a macula clinic (group 2; $n = 132$ eyes) over 24 months.

Results Baseline characteristics of the patients in the two groups, including age, initial BCVA (group 1 58.2 ± 18.5, group 2 60.8 ± 16.1 ETDRS letters; $p = 0.32$), and baseline CRT, were comparable. By end of the observation period, both groups presented similar BCVA (group 1 67.4 ± 19.3, group 2 66.8 ± 17.2 letters; $p = 0.51$), visual gains (group 1 7.8 ± 16.9, group 2 5.8 ± 14.4 letters; $p = 0.11$), CRT values (group 1 259.6 ± 80.5, group 2 277.4 ± 87.1 μm; $p = 0.10$), and number of injections (group 1 13.0 ± 4.5, group 2 11.6 ± 4.1 injections; $p = 0.09$), as well as portion of eyes with stable disease (absence of any intraretinal fluid and absence or stability of subretinal fluid and pigment epithelial detachment: group 1 78% ($n = 128$), group 2 75% ($n = 95$); $p = 0.63$). However, there was a significant difference regarding the number of examinations (group 1 12.8 ± 5.0, group 2 9.7 ± 3.1 visits; $p = 0.0005$).

Conclusions nAMD treatment delivered by practice-based ophthalmologists is reasonable regarding functional outcomes and reduces the indirect treatment burden, which is partially outweighed by significantly more clinical examinations in ophthalmological practices.

Keywords Exudative age-related macular degeneration · Choroidal neovascularization · Ranibizumab · Aflibercept · Treat and extend · Delegation · Treatment burden

Introduction

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections are the most effective and well-established treatment option for neovascular age-related macular degeneration (nAMD) and have become the gold standard of care [1–5]. Despite highly satisfactory clinical results, frequent examinations and intravitreal anti-VEGF injections are necessary over a prolonged period, which can become demanding for older patients, particularly when treatment is not available in the vicinity of their homes. Specialized macula clinics are currently dealing with an increasing number of nAMD patients. Despite the development and implementation of new standardized treatment strategies, such as the treat-and-extend (T&E) protocol, this increase places demands based on frequently limited resources [6–10]. Larger clinics have addressed this issue by establishing trainee- or nurse-led intravitreal injection services [11–13]. In this setting, the treatment decision remains with the treating physician. Therefore, an upcoming adaptation of care services due to the rising demand for nAMD treatment appears unavoidable. The increasing age

✉ Justus G. Garweg
Justus.garweg@swiss-eye-institute.com

[1] Berner Augenklinik am Lindenhofspital, Rotkreuz, Switzerland

[2] Department Ophthalmology, University Hospital Bern, Bern, Switzerland

[3] Swiss Eye Institute, Bremgartenstrasse 119 CH - 3012 Bern, Switzerland

Published online: 08 April 2020

and polymorbidity of many nAMD patients may limit the ability to gain access to examinations and injections. Therefore, treatment opportunities in close proximity to patients are desirable from the patient perspective. Accordingly, this may improve cost-effectiveness, especially regarding secondary social costs, such as transportation by family members. Since macula clinics may have a limited treatment capacity for the increasing number of new cases, the delegation of examinations and injections is a valuable option. Accordingly, the present study compared the outcomes of patients treated for nAMD under the care of a practice-based ophthalmologist and in a specialized macula clinic.

Methods

Participants

This retrospective, interventional consecutive case series included treatment-naïve eyes with nAMD of patients treated with their first intravitreal anti-VEGF injection between January 2016 and July 2018, with a minimal follow-up of 12 months. The patients received either ranibizumab (Lucentis®, Novartis) or aflibercept (Eylea®, Bayer) at the discretion of the treating physician, according to a T&E protocol. The protocol included a loading phase of a minimum three monthly injections until complete disappearance of intraretinal and absence or stability of subretinal fluid and pigment epithelial detachment. Thereafter, extension of the examination and treatment intervals was adjusted by 2 weeks at each visit up to a maximum of 14 weeks to maintain lesion stability in the absence of new or recurrent fluid in optical coherence tomography (OCT). Patients were expected to receive treatment at each visit; however, a treatment interruption was provided in cases presenting with lesion stability for more than 6 months. This treatment protocol was strictly followed by our institution and adherence to this protocol confirmed by the practice-based ophthalmologists, but not independently controlled.

Excluded were patients not responding to or providing informed consent to the use of their coded data ($n = 42$), eyes with inadequately controlled glaucoma (intraocular pressure > 21 mmHg under maximal therapy), retinal detachment, retinal vascular disease (i.e., retinal vein occlusion, central retinal artery occlusion, or potentially relevant diabetic retinopathy), any history of posterior segment surgery, history of or present uveitis, and anti-VEGF pre-treatment without a complete loading phase of three monthly injections. Reasons for treatment discontinuation and loss-to-follow-up were recorded.

Ethics

This study strictly adhered to the tenets of the Declaration of Helsinki and approved by the Institutional Ethics Committee of the University of Bern (reference number: 2019-01265). Informed consent was obtained from patients prior to inclusion in the study for the use of their coded data.

Setting

Group 1 included 215 eyes from patients referred to the macula clinic from practice-based ophthalmologists for confirmation of diagnosis according to local guidelines, including fluorescein angiography, if possible, or with the diagnosis made by the referring ophthalmologist. The referring ophthalmologist performed all clinical examinations and treatments after diagnosis. Twenty-eight practice-based ophthalmologists contributed to the study, with each providing data from 1 to 31 patients. Group 2 included a consecutive series of 132 eyes with newly diagnosed nAMD that had received treatment with either ranibizumab (Lucentis®, Novartis) or aflibercept (Eylea®, Bayer) in the macula clinic of the Berner Augenklinik am Lindenhofspital, Bern.

Data collection

In group 1, all referring ophthalmologists were requested to extract a data set for the affected eyes on a predefined paper matrix corresponding to the data set to be retrieved from the clinic's electronic case records as detailed below. Alternatively, ophthalmologists were also provided with the option to request support from a member of the research team from the Berner Augenklinik am Lindenhofspital concerning data extraction from the medical records and OCT databases, which was performed by a staff member of the ophthalmological practice. Ophthalmologists that routinely performed a minimum of 100 injections per year were selected. To minimize sampling and recording errors, each ophthalmologist received instructions, including examples of correct data collection, as well as a predetermined list of patients to minimize potential selection bias. Data were controlled for accuracy and completeness before input into the secured database. The type of OCT device, treatment protocol, and the estimated total number of injections administered annually were requested from each ophthalmologist. BCVA and CRT were recorded at baseline and 3, 6, 12, and 24 months after initiating anti-VEGF treatment. The type of anti-VEGF treatment used at initiation (switchers were not registered), as well as the number of injections and visits, was extracted from electronic medical records.

BCVA is routinely tested on a logarithmic Snellen scale using a projection system and converted to Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores with 85 letters representing a BCVA of 1.0. If the patient was unable to recognize all letters in a line, the corresponding fraction was documented and used for conversion to ETDRS letter scores. OCT was used to manually measure the CRT in the foveola

Table 1 Baseline characteristics of patients treated by ophthalmologist in private practice (group 1) or in the macula clinic (group 2)

	Group 1	Group 2	*p* value
Number of eyes/patients	215/203	132/129	
Female patients (%)	59.8	58.3	0.82
Age (years, mean ± SD)	80.6 ± 7.4	80.3 ± 6.8	0.79
Baseline BCVA (ETDRS letters, mean ± SD)	58.2 ± 18.5	60.8 ± 16.1	0.32
Baseline CRT (μm, mean ± SD)	382.9 ± 126.1	397.7 ± 130.8	0.20
Ranibizumab (%)	30.8	32.6	0.81
Aflibercept (%)	69.2	67.4	
Lost to follow-up, *n* (%)	19 (8.9)	6 (5.2)	0.10

BCVA, best-corrected visual acuity; *ETDRS*, Early Treatment of Diabetic Retinopathy Study scores with 85 letters representing a gain in best-corrected visual acuity of 1.0; *CRT*, central retinal thickness; *SD*, standard deviation. Statistical methods: Mann-Whitney *U* test for group comparison in interval scaled data and chi-square test for group comparison with nominal scaled data

from the inner retinal surface to Bruch's membrane. To be recorded as a clinical visit, the clinical examination included BCVA and OCT measurements as the basis for treatment decisions. Post-injection controls were not performed routinely by most centres and not recorded. Coded data were collected in a secured database.

Outcomes

The primary endpoint was change in BCVA. Secondary endpoints included the evolution of CRT under therapy, the number of injections and visits over 24 months, the number of eyes unable to achieve disease stability under treatment (defined as the presence of any intraretinal fluid or instability of subretinal fluid or pigment epithelial detachment), and treatment adherence.

Statistics

Numerical data are presented as mean values ± the standard deviation (SD). Nonparametric tests were used for data analysis, as data were not normally distributed. The Mann-Whitney *U* test and chi-square test were used for group comparisons. A *p* value of < 0.05 was considered statistically significant.

Results

The present study involved a consecutive series of 347 treatment-naïve eyes from 332 patients (group 1: $n = 215$; group 2: $n = 132$). Group 1 was treated by 28 practice-based ophthalmologists experienced in the treatment of macular diseases (> 100 injections per year), whereas group 2 was treated in the specialized macula clinic. Twenty-eight practice-based ophthalmologists provided data from a mean of 10.0 (± 7.6; 1 to 27) eyes per ophthalmologist. The same T&E protocol was agreed on by all practice-based ophthalmologists and the clinic. Six different OCT devices were used (Spectralis™, Heidelberg Engineering, Heidelberg, Germany; REVO NX, Optopol Technology SA, Zawiercie, Poland; RS3000, Nidek CO., LTD, Tokyo, Japan; iVue®, Optovue Inc., Fremont, CA, USA; Triton and 3D Maestro, Topcon, Tokyo, Japan) with only one device applied in the clinic (OCT, Spectralis™, Heidelberg Engineering, Heidelberg, Germany). There were no significant differences between the two groups with regard to gender, age, initial BCVA, baseline CRT, intravitreal drug, and loss-to-follow-up after treatment initiation (Table 1). Moreover, visual gains (Table 2), BCVA (Fig. 1), and CRT (Fig. 2), as well as the number of injections, did not differ between the groups over the observation period. A significantly higher number of clinical examinations were observed for group 1, with a difference of

Table 2 Gain in best-corrected visual acuity

ETDRS letters ± SD	*n*	Group 1	*n*	Group 2	*p* value
From baseline to 12 months	214	9.5 ± 15.4	131	7.2 ± 14.8	0.10
After loading phase to 12 months	214	− 0.3 ± 12.4	131	− 0.1 ± 8.5	0.81
From baseline to 24 months	126	7.8 ± 16.9	97	5.8 ± 14.4	0.11
After loading phase to 24 months	126	− 2.1 ± 14.2	97	− 1.0 ± 10.2	0.89

BCVA, best-corrected visual acuity; *ETDRS*, Early Treatment of Diabetic Retinopathy Study scores with 85 letters representing a gain in best-corrected visual acuity of 1.0; *SD*, standard deviation. Statistical methods: Mann-Whitney *U* test for group comparison

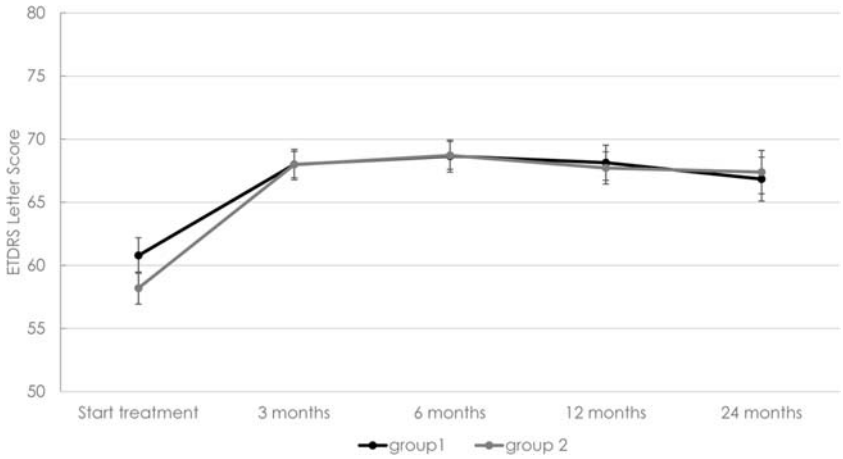

Fig. 1 Best-corrected visual acuity (BCVA in EDTRS letters) before treatment initiation as well as after 3, 6, 12, and 24 months. Black line: group 1, grey line: group 2. The Mann-Whitney *U* test was used for group comparisons. ETDRS (Early Treatment of Diabetic Retinopathy Study) scores with 85 letters representing a score in best-corrected visual acuity (BCVA) of 1.0

32% compared with group 2 (Table 3). Persistent disease activity was similar in both groups. Differentiation of outcomes based on the type of anti-VEGF treatment revealed a lower portion of disease activity after the loading phase in patients treated with aflibercept; however, this effect did not persist (Tables 4 and 5).

Discussion

Similar treatment success was observed in both patient groups treated either by practice-based ophthalmologists or in the specialized macula clinic. These results correspond with previous reports on the visual outcome, evolution of CRT, number of visits, and number of injections [14–27]. Results were achieved through in-house training of most practice-based ophthalmologists and long-lasting cooperation between the referring physician and the clinic, and are based on a comparable number of injections following the same treatment protocol.

The most notable difference was the consistently higher number of clinical examinations in group 1 over the entire follow-up period. The difference in the number of visits during the loading phase can be explained by the fact that patients in the clinic received three loading injections without intercurrent examination, whereas practice-based ophthalmologists scheduled an examination before every injection during the loading phase despite the absence of a need for treatment decisions. A comparison of the number of first-year visits after the loading phase between both groups revealed a persistent, significant difference (Table 3). This effect could be attributed to a higher decision-making certainty in the high-throughput clinic or other yet unidentified factors.

Treatment adherence was excellent in both groups; however, the reason for treatment interruption was not recorded in most group 1 patients (16/26). In contrast, patients in our clinic that missed appointments were contacted systematically and, if desired, offered new appointments. The most common reason for treatment discontinuation (4/10) was the absence of a visual potential despite stable OCT findings. Corresponding patients were referred back to their practice-based ophthalmologists for

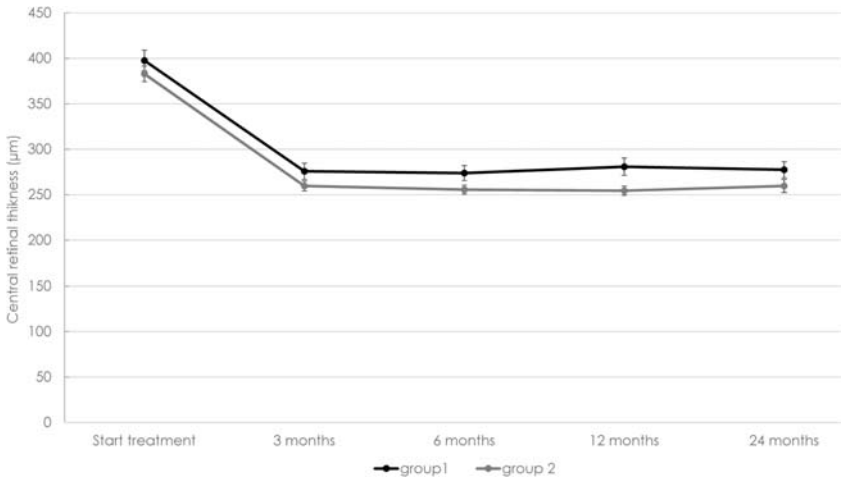

Fig. 2 Central retinal thickness (CRT in µm) before treatment initiation, and after 3, 6, 12, and 24 months. Black line: group 1; grey line: group 2. The Mann-Whitney *U* test was used for group comparisons

Table 3 Clinical examinations and treatment demand

	Group 1			Group 2			*p* value
	n	Mean	SD	*n*	Mean	SD	
Clinical examinations							
Year 1	215	8.8	2.4	132	6.0	1.5	0.0005
After loading phase, year 1	215	6.0	2.1	132	3.9	1.4	0.0005
Year 2	131	6.5	2.8	96	5.2	1.3	0.0005
Total	215	12.8	5.0	132	9.7	3.1	0.0005
Injections							
Year 1	215	8.0	2.1	132	7.7	1.5	0.23
After loading phase, year 1	215	5.0	2.0	132	4.9	1.3	0.87
Year 2	131	5.2	2.8	97	5.6	2.4	0.15
Total	215	11.1	4.4	132	11.8	3.8	0.10

SD, standard deviation

follow-up. Four patients (1%) died during the observation period (three in group 1, one in group 2). In two cases, treatment was stopped due to a severe systemic co-morbidity.

The use of different OCT devices could potentially limit the reproducibility of measurements as previously reported. However, this effect was negligible because all measurements were performed manually instead of using automated CRT measurements, and a comparison of measurements at the macula clinic and referring ophthalmologists revealed a < 10% difference within the same patients [28]. To our knowledge, this is the first study evaluating treatment by practice-based ophthalmologists compared with treatment at a macula clinic which confirmed these findings. Michelotti et al. showed a nurse substituting injection system to be safe and well-tolerated [12]. A comparison of specialist- and trainee-led management also revealed no significant difference in outcomes over 36 months with similar numbers of injections and visits as in our study [11].

A follow-up of the 3935 injections performed in this study did not reveal endophthalmitis in either group. Despite careful instruction before study initiation and data collection as described above, the involvement of 28 specialists may represent a potential bias in data collection and cannot be completely ruled out. Furthermore, a larger sampling size could lead to more accurate results.

In conclusion, a decade after the introduction of anti-VEGF treatment for the treatment of nAMD, this therapy has achieved a high level of treatment success based on the use of the widely accepted T&E protocol and ubiquitous availability of OCT devices. Treatment of patients with nAMD by practice-based ophthalmologists appears reliable and does not encompass disadvantages for the patient, whereas newly marketed treatments and protocols should be initiated and examined in larger expert centres.

Table 4 Presence of disease activity (disease activity: presence of any intraretinal fluid and/or new presence or instability of subretinal fluid or pigment epithelial detachment)

	Group 1	Group 2	*p* value
3 months (*n* present/*n* total (%))	63/215 (29)	44/132 (33)	0.47
6 months (*n* present/*n* total (%))	51/215 (24)	39/132 (29)	0.26
12 months (*n* present/*n* total (%))	48/215 (22)	43/132 (33)	0.06
24 months (*n* present/*n* total (%))	28/128 (22)	24/95 (25)	0.63

Table 5 Comparisons of disease activity (disease activity: presence of any intraretinal fluid and/or new presence or instability of subretinal fluid or pigment epithelial detachment) between aflibercept and ranibizumab

	Aflibercept	Ranibizumab	*p* value
3 months (*n* present/*n* total (%))	63/237 (27)	44/110 (40)	0.012
6 months (*n* present/*n* total (%))	55/237 (23)	35/110 (32)	0.09
12 months (*n* present/*n* total (%))	60/237 (25)	31/110 (28)	0.60
24 months (*n* present/*n* total (%))	32/149 (21)	20/74 (27)	0.40

Acknowledgements The publication was made possible through the co-operation of the 28 ophthalmologists working in practices in our region, including R. Adam, I. Bleuel, M. Bodenmüller, D. Domig, B. Frank, M. Hablützel, C. Häusler, P. Käser, B. Kopp, D. Lehmann, P. Marti, M. Mathieu, S. Niderprim, B. Perren, T. Romppainen, D. Sollberger, M. Tarek, P. Trittibach, M. vanSon, M. Wegmann, A. Wild, D. Zürcher, and a further six anonymous ophthalmologists.

Compliance with ethical standards

Ethical approval All procedures performed with studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees 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.

Conflict of interest JGG advises several pharmaceutical companies (Alcon, Allergan, Bayer, Novartis) and participates in a number of international, multicentre clinical studies in the fields of AMD and diabetic retinopathy that are sponsored by some of these companies (Chengdu Kanghong, Novartis, and Bayer). These activities had no bearing on the study that gave rise to the submitted article for which JGG received neither direct nor indirect financial support; nor does he have any conflicts of interest regarding the presented data. The other authors have no potential conflicts of interest to report.

References

1. Brown DM, Michels M, Kaiser PK et al (2009) Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related

macular degeneration: two-year results of the ANCHOR Study. Ophthalmology. 116:57–65. https://doi.org/10.1016/j.ophtha.2008.10.018
2. Rosenfeld PJ, Brown DM, Heier JS et al (2006) Ranibizumab for neovascular age related macular degeneration. N Engl J Med 355:1419–1431. https://doi.org/10.1056/NEJMoa054481
3. Heier JS, Brown DM, Chong V et al (2012) Intravitreal aflibercept (VEGF trap-eye) in neovascular age-related macular degeneration. Ophthalmology 119(12):2537–2548. https://doi.org/10.1016/j.ophtha.2012.09.006
4. Comparison of Age-related Macular Degeneration Treatments Trials (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. 119:1388–1398. https://doi.org/10.1016/j.ophtha.2012.03.053
5. Rofagha S, Bhisitkul RB, Boyer DS, Sadda SR, Zhang K, SEVEN-UP Study Group (2013) Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). Ophthalmology 120(11):2292–2299. https://doi.org/10.1016/j.ophtha.2013.03.046
6. Wong WL, Su X, Li X et al (2014) Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health 2(2):e106–e116. https://doi.org/10.1016/S2214-109X(13)70145-1
7. Colijn JM, Buitendijk GHS, Prokofyeva E et al (2017) EYE-RISK consortium, European Eye Epidemiology (E3) consortium. Prevalence of age-related macular degeneration in Europe: the past and the future. Ophthalmology 124:1753–1763. https://doi.org/10.1016/j.ophtha.2017.05.035
8. Wykoff CC, Ou WC, Croft DE et al (2018) Group T-AS: Neovascular age-related macular degeneration management in the third year: final results from the TREX-AMD randomised trial. Br J Ophthalmol 102:460–464. https://doi.org/10.1136/bjophthalmol-2017-310822
9. DeCroos FC, Reed DC, Adam MK et al (2016) Prospective, multicentre investigation of aflibercept treat and extend therapy for neovascular age related macular degeneration (ATLAS study): one and two year results. Abstract presented at: the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting; Seattle
10. Barthelmes D, Nguyen V, Daien V et al (2018) Two year outcomes of 'treat and extend' intravitreal therapy using aflibercept preferentially for neovascular age related macular degeneration. Retina. 38(1):20–28. https://doi.org/10.1097/IAE.0000000000001496
11. Essex RW, Nguyen V, Daien V et al (2019) Trainee-led versus specialist-led management of neovascular age-related macular degeneration: a registry-based study. Br J Ophthalmol 103(8):1158–1162. https://doi.org/10.1136/bjopthalmol-2018-311852
12. Michelotti MM, Abugreen S, Kelly SP et al (2014) Transformational change: nurses substituting for ophthalmologists for intravitreal injections - a quality-improvement report. Clin Ophthalmol 8:755–761. https://doi.org/10.2147/OPTH.S59982
13. Samalia P, Garland D, Squirrell D (2016) Nurse specialists for the administration of antivascular endothelial growth factor intravitreal injections. N Z Med J 129:32–38
14. Chakravarthy U, Harding P, 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. https://doi.org/10.1016/SO140-6736(13)61501-9
15. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF et al (2014) Intravitreal aflibercept injection for neovascular age related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology. 121:193–201. https://doi.org/10.1016/j.ophtha.2013.08.011
16. Engelbert M, Zweifel SA, Freund KB (2009) "Treat and extend" dosing of intravitreal antivascular endothelial growth factor therapy for type 3 neovascularization/retinal angiomatous proliferation. Retina 29:1424–1431. https://doi.org/10.1097/IAE.0b013e3181bfbd46
17. Engelbert M, Zweifel SA, Freund KB (2010) Long-term follow-up for type 1 (subretinal pigment epithelium) neovascularization using a modified "treat and extend" dosing regimen of intravitreal antivascular endothelial growth factor therapy. Retina. 30:1368–1375. https://doi.org/10.1097/IAE.0b013e3181d50cbf
18. Gupta OP, Shienbaum G, Patel AH et al (2010) A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact. Ophthalmology. 117:2134–2140. https://doi.org/10.1016/j.ophtha.2010.02.032
19. Shienbaum G, Gupta OP, Fecarotta C et al (2012) Bevacizumab for neovascular age-related macular degeneration using a treat and-extend regimen: clinical and economic impact. Am J Ophthalmol 153:468–473. https://doi.org/10.1016/j.ajo.2011.08.011
20. Fung AT, Kumar N, Vance SK et al (2012) Pilot study to evaluate the role of high-dose ranibizumab 2.0 mg in the management of neovascular age-related macular degeneration in patients with persistent/recurrent macular fluid, 30 days following treatment with intravitreal anti-VEGF therapy (the LAST Study). Eye (Lond) 26:1181–1187. https://doi.org/10.1038/eye.2012.174
21. Toalster N, Russell M, Ng PA (2013) A 12-month prospective trial of inject and extend regimen for ranibizumab treatment of age related macular degeneration. Retina. 33:1351–1358. https://doi.org/10.1097/IAE.0b013e3182831265
22. Abedi F, Wickremasinghe S, Islam AF, Inglis KM, Guymer RH (2014) Anti-VEGF treatment in neovascular age-related macular degeneration: a treat and-extend protocol over 2 years. Retina 34(8):1531–1538. https://doi.org/10.1097/IAE.0000000000000134
23. Rush RB, Simunovic MP, Vandiver L, Aragon AV 2nd, Ysasaga JE (2014) Treat-and-extend bevacizumab for neovascular age-related macular degeneration: the importance of baseline characteristics. Retina. 34(5):846–852. https://doi.org/10.1097/IAE.0000000000000033
24. Rush RB, Rush SW, Aragon AV 2nd, Ysasaga JE (2014) Evaluation of choroidal neovascularization with indocyanine green angiography in neovascular age-related macular degeneration subjects undergoing intravitreal bevacizumab therapy. Am J Ophthalmol 158(2):337–344. https://doi.org/10.1016/j.ajo.2014.05.007
25. Berg K, Pedersen TR, Sandvik L, Bragadottir R (2015) Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol. Ophthalmology. 122:146–152. https://doi.org/10.1016/j.ophtha.2014.07.041
26. Rayess N, Houston SK III, Gupta OP et al (2015) Treatment outcomes after 3 years in neovascular age-related macular degeneration using a treat-and-extend regimen. Am J Ophthalmol 159(1):3–8. https://doi.org/10.1016/j.ajo.2014.09.011
27. Arnold JJ, Campain A, Barthelmes D et al (2015) Two-year outcomes of "treat and extend" intravitreal therapy for neovascular age-related macular degeneration. Ophthalmology. 122(6):1212–1219. https://doi.org/10.1016/j.ophtha.2015.02.009
28. Wolf-Schnurrbusch UE, Ceklic L, Brinkmann CK et al (2009) Macular thickness measurements in healthy eyes using six different optical coherence tomography instruments. Invest Ophthalmol Vis Sci 50(7):3432–3437. https://doi.org/10.1167/iovs.08-2970