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EXIT STRATEGY IN A TREAT-AND-EXTEND REGIMEN FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION

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Purpose: To evaluate the outcome of an exit strategy in a treat-and-extend regimen for neovascular age-related macular degeneration.

Methods: Five hundred and ninety-eight eyes of 488 patients with neovascular age-related macular degeneration receiving intravitreal anti–vascular endothelial growth factor injections according to a treat-and-extend regimen were included in this retrospective study. A treat-and-extend regimen with either interval extension by 2 weeks or shortening by 1 week was used. "Exit criteria" were defined as 3 consecutive injections 16 weeks apart with stable findings after which the patient was exited from treatment and followed up at 3 to 4 monthly intervals without therapy. Best-corrected visual acuity, central retinal thickness at treatment initiation and termination, incidence of recurrence after treatment termination, presence of characteristics in the optical coherence tomography, duration of therapy, number and intervals of injections were analyzed.

Results: Seventeen percent of all included eyes met the exit criteria. The mean number of anti–vascular endothelial growth factor injections was 23.7 ± 14.7 with a mean treatment duration of 4.5 ± 2.5 years. Twelve percent reached exit with the minimal number of injections. Thirteen percent had recurrent disease after a mean of 37 ± 16 weeks. In the subgroup with recurrent disease, rate of pigment epithelial detachment at treatment termination was significantly higher than without recurrence (77% vs. 30%, $P = 0.0018$) with a significant higher proportion of serous pigment epithelial detachment (31% vs. 7%, $P = 0.0247$).

Conclusion: The high percentage of patients meeting the exit criteria and the relatively low incidence of recurrences underline the usefulness of a predefined exit strategy. However, in a subgroup of patients, continuation of therapy may be advisable.

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Age-related macular degeneration (AMD) is a major cause of visual impairment in elderly people in the Western world.[1,2] Risk factors include smoking, eating habits, genetic background, and recently an association with the gut microbiome has been demonstrated.[3–5] The development of choroidal neovascularization secondary to AMD is an attribute of exudative AMD. The pivotal trials for exudative AMD have shown that monthly or bimonthly injections lead to an excellent functional and anatomical outcome. However, subsequent trials have found that these results were not maintained after switching to a pro re nata (PRN) regimen, and long-term studies have shown that the initial gain in visual acuity is largely obliterated after 5 years of treatment.[6,7]

We have recently analyzed outcomes of our patients when terminating a PRN regimen.[8] We found that only 2.6% of patients were able to terminate treatment after reaching predefined exit criteria. These criteria required 3 monthly injections for 1 year, followed by 2 injections 6 months apart in the second year with stable disease, defined as no intraretinal fluid (IRF) or subretinal fluid (SRF).

To reduce treatment burden and the need for monthly follow-ups, the treat-and-extend regimen has become popular in recent years. In this treatment regimen, administration of injections is guided by optical coherence tomography (OCT) findings with either extension or decrease of treatment intervals, depending on disease activity.[9] Although the extension and decrease of

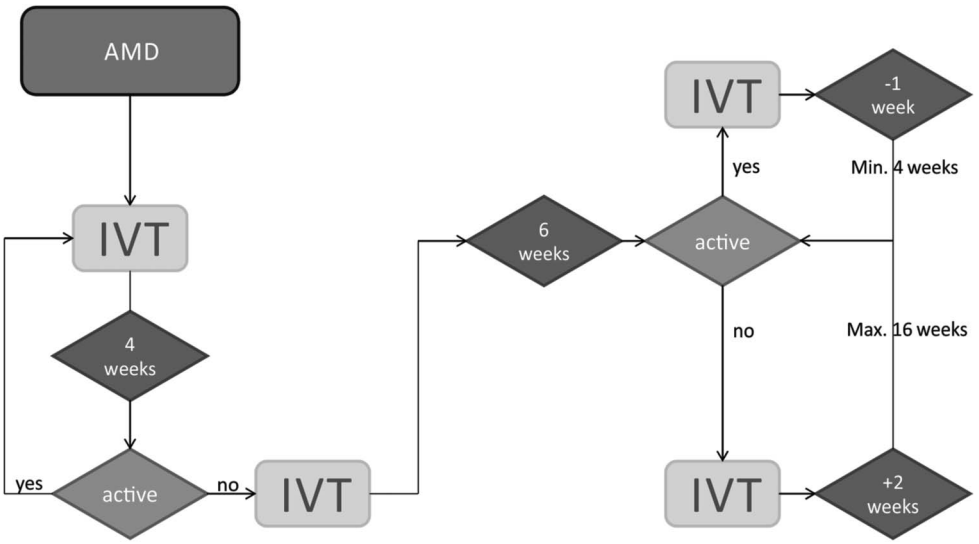

Fig. 1. Outline of the Bern treat-and-extend regimen for AMD: Four weeks after the first intravitreal injection (IVT) with an anti-VEGF, a second injection is given. Depending on the OCT findings, the interval to the following injection is adjusted. The treatment interval is extended by 2 weeks if stable disease is present or shortened, respectively, by 1 week if there are signs of activity, defined as IRF and/or SRF. When the interval had to be shortened, this interval must not be extended for the next 6 months but may be shortened in case of activity at any visit. After 6 months, the intervals can be extended again. The exit criteria are reached if the maximal interval of 16 weeks is reached and maintained for 3 consecutive injections.

intervals seems to be quite uniform in published reports,[10–12] there is still considerable debate about which maximum interval is reasonable and there is little, if none, data on outcomes of exit strategies when treating patients with a treat-and-extend approach. In the treat-and-extend regimen used at our institution, the maximal interval is 16 weeks, and "exit criteria" are defined as 3 consecutive injections with an interval of 16 weeks with stable findings. "Exit" describes the termination of anti–vascular endothelial growth factor (VEGF) treatment after reaching the exit criteria.

The aim of this retrospective study was to evaluate the outcome of a predefined exit strategy using a treat-and-extend regimen for exudative AMD.

Methods

Patient Selection

Patients with neovascular AMD receiving intravitreal injections under a treat-and-extend regimen with ranibizumab or aflibercept for exudative AMD were identified in our institutional database at the Department of Ophthalmology at the University Hospital Bern, Switzerland. Ethics approval (KEK-Nr. 093/13) to conduct this study was obtained from the local ethics committee, which is working in accordance with ICH-GCP guidelines. The study was conducted in compliance with the tenets of the Declaration of Helsinki.

None of the patients had previous photodynamic therapy. Subjects who had discrepancies of more than 2 weeks between the scheduled visit and the effective visit were excluded from the evaluation of the treatment intervals. Patients who reached the exit criteria until August 31, 2016, were identified, and the number of injections, duration of therapy, and intervals between the injections were analyzed.

Treat-and-Extend Regimen

An outline illustrating the Bern treat-and-extend regimen is shown in Figure 1. Briefly, in this regimen, patients receive an injection at each visit in addition to early treatment diabetic retinopathy study (ETDRS) visual acuity testing and spectral domain OCT imaging (Heidelberg Engineering, Heidelberg, Germany). All patients receive a second anti-VEGF injection 4 weeks after the first injection. Depending on the findings in OCT and on ETDRS visual acuity, the intervals are then adjusted as follows: The treatment interval is extended by 2 weeks if stable disease is present. Stable disease is defined as no evidence of intra–retinal pigment epithelium (RPE), subretinal RPE, or sub-RPE fluid in the OCT; SRF below the fovea <50 μm (measured with digital calipers) and no change in subretinal RPE and sub-RPE fluid and

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stable visual acuity at the third consecutive examination (within five ETDRS letters of either of the last three visits). A localized pigment epithelial detachment (PED) was not attributed to disease activity and would allow for further extension of treatment intervals. The interval to the next injection is to be shortened by 1 week if there are signs of activity. When the interval had to be shortened and stable disease is seen in 2 following examinations, this interval must not be extended for the next 6 months. After 6 months, the intervals can be extended again after the treat-and-extend regimen.

The exit criteria are defined as follows: when the interval is extended to 16 weeks and the findings are stable, the interval of 16 weeks is maintained for 3 consecutive injections before therapy is stopped. Subsequently, only follow-up visits are planned every 3 to 4 months.

According to this regimen, the minimal number of injections from the start of therapy to the exit is 10, with a minimum duration of therapy of about 2 years (Figure 2).

Best-corrected visual acuity (BCVA) and central retinal thickness (CRT) at initiation and termination of treatment, the number of injections and intervals between the injections, duration of therapy as well as the incidence of recurrence after termination of treatment were investigated.

Evaluation of Optical Coherence Tomography Characteristics

The presence or absence of characteristics in the OCT images was identified for all patients who fulfilled the exit criteria including: atrophy, subretinal hyperreflective material, IRF or SRF, and PED. These characteristics were defined as the following: IRF was identified as hyporeflective spaces within the neurosensory retina of >25 μm, whereas SRF was defined as a nonreflective space between the RPE and the posterior boundary of the neurosensory retina. A PED was identified as an elevation of the RPE band and included serous (evidenced by hyporeflective internal reflectivity) as well as fibrovascular PED (evidenced by heterogeneous internal reflectivity). Atrophy was defined as a sharply delineated area with loss of the RPE band and consequent hyperreflectivity of the choriocapillaris. Continuous hyperreflective subretinal tissue between neurosensory retina and Bruch membrane was described as "subretinal hyperreflective material". Optical coherence tomography images were analyzed at initiation and termination of treatment.

Statistical Analysis

Data analysis was performed using GraphPad Prism version 5.02 for Windows (GraphPad Software, La Jolla, CA), www.graphpad.com.

Significance testing for the differences in OCT characteristics of the subgroups was performed using Fisher's exact test. To compare the changes in BCVA and CRT within all included eyes, a paired *t*-test was used, and to compare differences in the mean changes of BCVA and CRT in the subgroups, an unpaired *t*-test was used. A P value less than 0.05 was stated as significant.

Results

A total of 655 eyes of 533 patients treated with ranibizumab or aflibercept within the period between January 1, 2014, and December 31, 2015, were identified. Fifty eyes had to be excluded with less than 3 injections and 7 eyes that were switched either to aflibercept or ranibizumab. The inclusion criteria were met by 598 eyes of 488 patients.

The mean age was 80 ± 9 years (range 50–95 years), about two-thirds of the patients were female (63%). Seventeen percent (100 eyes) of all included eyes of 95 patients met the exit criteria. The demographic data of patients who met the exit criteria were comparable with the entire patient cohort in this study, with a mean age of 80 ± 9 years (range 51–92 years) and 64% female patients. In the patient cohort, meeting the exit criteria, the mean number of anti-VEGF injections was 23.7 ± 14.7 with a mean treatment duration of 236 ± 130 weeks (4.5 ± 2.5 years). Fluorescein angiography before treatment revealed 59 cases (59%) of occult

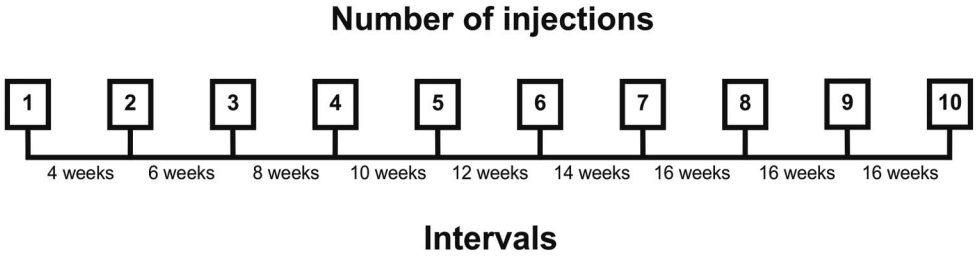

Fig. 2. Outline of the minimal number of injections (10) according to the treat-and-extend regimen from the start of therapy to the exit with a minimum duration of therapy of about 2 years.

choroidal neovascularization, 30 cases (30%) of predominantly classic choroidal neovascularization, and 2 cases (2%) of polypoidal choroidal vasculopathy. In nine cases (9%), no fluorescein angiography was performed before treatment, and diagnosis was based on OCT.

There was no significant change in BCVA from the start to termination of therapy (62.2 ± 13.3 vs. 62.2 ± 17.5, $P = 0.80$), whereas CRT decreased significantly until the exit criteria were reached (366 ± 104 μm vs. 271 ± 55 μm, $P < 0.0001$).

Twelve eyes (of 12 patients) received a minimal number of 10 injections (12% of all eyes that met the exit criteria). This group of patients is called "rapid responders" in the following. The OCT characteristics for the groups of rapid and nonrapid responders including presence of PED, IRF and SRF, subretinal hyperreflective material, and atrophy are listed in Table 1A at start and in Table 1B at termination of therapy. In the group of nonrapid responders, 30% of the OCT images at the start of therapy could not be evaluated because of the use of another OCT device before 2009 (images were not available). In the group of rapid responders, all initial OCTs were available.

Thirteen eyes (of 12 patients), which reached exit criteria, had recurrent disease after treatment termination. The mean duration of follow-up for all 100 eyes that met the exit criteria was 40.5 ± 26.6 weeks. Patients presenting with recurrent disease after a mean of 37 ± 16 weeks had a mean loss of −3.7 ± 15.9 ETDRS letters, with 2 patients presenting with a loss of more than 15 letters. None of the rapid responders showed recurrent disease activity within the observation period. The OCT characteristics for the subgroups with and without recurrence are listed in Table 2A at start and in Table 2B at termination of therapy, respectively. The only significant difference between the two groups was the presence of PED at the time point of treatment termination (77% vs. 30%, $P = 0.0018$) with a significant higher proportion of serous PED (31% vs. 7%, $P = 0.0247$).

Changes of the mean of BCVA and CRT between the subgroups rapid versus nonrapid responders and recurrent disease versus nonrecurrent disease were not significant: 6.1 ± 6.9 versus −0.4 ± 15.0 letters ($P = 0.15$) and −105.0 ± 103.6 versus −99.5 ± 117.3 μm ($P = 0.88$), respectively, −4.9 ± 19.7 versus 1.2 ± 13.2 letters ($P = 0.16$) and −40.8 ± 148.0 versus −107.7 ± 108.2 μm ($P = 0.12$).

Discussion

In this study, we analyzed the outcomes of an exit strategy in a treat-and-extend regimen for exudative AMD. An unexpectedly high proportion of eyes (17%) met these exit criteria. This is a considerably larger portion in comparison with our findings in 2014 where only 2.6% of patients terminated treatment according to predefined exit criteria using a capped PRN treatment approach.[8] To understand this discrepancy, the respective peculiarities of the PRN and the treat-and-extend regimen need to be discussed. The PRN regimen mandates monthly follow-ups with anti-VEGF therapy, given only if there is disease activity.

Table 1. Subgroup Analysis for Rapid and Nonrapid Responders

OCT Characteristic	Rapid Responders, %	Nonrapid Responders, %*	*P*†
A) OCT characteristics of exit patients when therapy was initiated			
PED	67	72	0.73
Serous	*17*	*36*	0.32
Fibrovascular	*50*	*36*	0.52
SRF	58	64	0.75
IRF	58	59	1.00
Subretinal hyperreflective material	33	13	0.10
Atrophy	42	26	0.31
OCT Characteristic	**Rapid Responders, %**	**Nonrapid Responders, %**	***P*†**
B) OCT characteristics of exit patients when therapy was terminated			
PED	17	39	0.20
Serous	*8*	*10*	1.00
Fibrovascular	*8*	*28*	0.18
SRF	0	7	1.00
IRF	0	0	
Subretinal hyperreflective material	75	60	0.53
Atrophy	75	82	0.45

*27/88 OCTs were missing (30.7%) at baseline.
†Statistical significance tested by Fisher's exact test.

Table 2. Subgroup Analysis for Patients With Respectively Without Recurrent Disease

OCT Characteristic	Recurrence, %*	No recurrence, %†	*P*‡
A) OCT characteristics of patients who fulfilled the exit criteria when therapy was first initiated			
PED	100	68	0.10
Serous	*63*	*29*	0.11
Fibrovascular	*38*	*39*	1.00
SRF	63	63	1.00
IRF	38	62	0.26
Subretinal hyperreflective material	0	19	0.34
Atrophy	13	31	0.43
OCT Characteristic	Recurrence, %	No Recurrence, %	*P*‡
B) OCT characteristics of patients who fulfilled the exit criteria when therapy was terminated			
PED	77	30	**0.0018**
Serous	*31*	*7*	**0.0247**
Fibrovascular	*46*	*23*	0.10
SRF	15	5	0.18
IRF	0	0	
Subretinal hyperreflective material	54	63	0.55
Atrophy	69	83	0.25

*5/13 OCTs were missing (38.5%).
†22/87 OCTs were missing (25.3%).
‡Statistical significance tested by Fisher's exact test.

By contrast, treatment intervals in the treat-and-extend regimen are adjusted according to the last follow-up and anti-VEGF treatment is mandatory at each visit. Several studies have shown, although there are less injections in the PRN regimen, that there are significantly more follow-up consultations than in the treat-and-extend regimen.[13–15] These differences between the two regimens provide possible explanations for the observed discrepancies. Because the PRN regimen requires monthly and therefore significantly more follow-up consultations with BCVA and OCT examinations than the treat-and-extend regimen,[16] especially during stable disease, patients or the treating physicians may be more inclined to stop treatment without reaching the predefined exit criteria. Aside from one study, which evaluated factors influencing patients' adherence in a PRN treatment regimen,[17] little is known about treatment compliance with anti-VEGF treatment and how compliance compares between different treatment regimens. However, in addition to patients' compliance, there are many other reasons why anti-VEGF is stopped. These include irreversible anatomical changes such as fibrovascular scar formation or RPE atrophy conflicting with further anti-VEGF treatment.

Another possible explanation is that patients may be undertreated in the PRN group with more disease recurrences. This, in turn, may have resulted in lower likelihood of reaching the predefined exit criteria in a PRN regimen. We have observed significantly less IRF or SRF after switching from a PRN regimen to a treat-and-extend regimen in a retrospective study.[15] Two meta-analyses investigating the "real-world" outcome of treat-and-extend versus PRN regimens in neovascular AMD further confirm the assumption that treat and extend may be superior compared with PRN treatment with higher numbers of administered injections, less disease activity, and better maintenance of visual function.[13,18]

Yet, another feature of the exit strategy merits further discussion. We are not aware of any consensus on the maximal treatment interval in a treat-and-extend regimen. Most studies have a maximal treatment interval of 12 weeks.[10–12] Ideally, the maximal treatment interval should allow to observe the patient under conditions when anti-VEGF levels have fallen below therapeutic levels. In a prospective clinical study, the mean suppression time after ranibizumab injections was determined to be approximately 36.4 days but showed a wide range between 26 and 69 days.[19] Aflibercept was shown to have a longer suppression time after injection of 70.5 ± 18.0 days with a range between 41 and 109 days.[20] As such, at least for ranibizumab, the minimal duration for the maximal interval would be set at 10 weeks, for aflibercept possibly up to 15 to 16 weeks. However, there is likely to be a delay between reaching subtherapeutic levels in the vitreous and disease recurrence and as such, a longer maximal interval is likely to result in better safety for patients.[21] However, it remains unclear which maximal treatment interval warrants for a stable level of VEGF suppression. It should be pointed out that in clinical practice, only the anatomical response is measured but not the VEGF levels. In comparison with

published treatment regimens,[10,12,22,23] we have used a longer maximal extension interval of 16 weeks. To evaluate sustained disease stability, this maximal interval of 16 weeks had to be maintained over the course of 1 year, before treatment could be terminated.

A large retrospective study showed that the risk of reactivation reached 37.4% at treatment intervals of ≥20 weeks. This would suggest that there is a considerable proportion of patients who would benefit from continued treatment at the maximum interval. However, these data contrast with our considerably lower recurrence rate of 13% after termination of treatment and a mean interval to recurrence since the last injection of approximately 9 months. One possible explanation could be the quite variable maximal treatment interval in the former study where intervals from 126 to 365 days were classified as 20 weeks.[24] Eyes with recurrence in our study only had an average loss of −3.7 ± 15.9 ETDRS letters, with only 2 eyes presenting with a loss of more than 15 letters. This suggests that only a very small percentage (2%) of eyes have a recurrence significantly affecting visual function when stopping treatment according to our exit criteria.

The same study reported that in the 86.5% of eyes treated with a treat-and-extend regimen and that never showed a reactivation, the injection interval could be extended to 12 weeks or more. But the risk of a disease recurrence was reported to increase with treatment intervals longer than 12 weeks, although the most common (17.4%) interval until reactivation reported was 8 weeks.[24]

In the analysis of the subgroups with respectively without recurrent disease, a significant higher rate of PED could be seen in the group with recurrences (77% vs. 30%, $P = 0.0018$) at termination of treatment. In the literature, PED was recently also described as the primary indicator reflecting progressive disease activity.[25] Waldstein et al[26] reported the highest rate of PED resolution in a monthly dosing regimen with aflibercept (39.5%) in comparison with a bimonthly dosing regimen with aflibercept and a monthly treatment with ranibizumab. These results imply that patients with PED need intensive anti-VEGF treatment and may require more long-term treatment than patients without persisting PED.

The mean BCVA change of all included eyes showed a wide range: changes between −47 and +33 letters were observed. This reflects the inhomogeneity within this group, especially about duration of treatment and also number of injections. However, the subgroup of rapid responders with a treatment duration of about 2 years showed a mean gain in BCVA of 6.1 ± 6.9 letters (range: −3 to +19 letters). Similar ranges of BCVA gains were reported in other treat-and-extend studies: mean BCVA gain after 1 year of 11.6,[27] 10.8,[16] 10.5,[10] 7,[23] 1.0 letters,[24] respectively, a mean BCVA change after 2 years of +10.7[27] and −0.6 letters.[24] Furthermore, it is comparable with the data of Menke et al[8] with a mean BCVA gain of 4.5 ± 16.9 letters in the group of patients who reached the exit criteria in a capped PRN treatment regimen based on the PIER study. Corresponding to a longer duration of treatment such as in the nonrapid responder group, a more pronounced BCVA loss would be expected. This is confirmed by the data of the SEVEN-UP study which reported a mean BCVA loss of −8.6 letters 7 years after treatment initiation.[6] Moreover, the CATT study data showed that after 5 years of anti-VEGF treatment, the initial vision gain could not be maintained.[7] The fact that initial gain of vision during the first year of treatment is lost in most long-term studies is in keeping with our data.

Limitations of this study include the small sample size and the retrospective design, which allows reporting of associations only. Time shifting of the planned visits occurred because of patients' liabilities or illness. This may have led to a possible inconsistency of treatment intervals. In addition, there is a small percentage of patients without initial OCT images.

Our data underline the fact that anti-VEGF treatment for neovascular AMD is useful and effective in preserving vision in many, but not all patients. There is still no cure for neovascular AMD and anti-VEGF treatment, confronts the physician with numerous unsolved problems such as unknown long-term side effects (i.e., geographic atrophy), and lacking of alternative treatment options or exit strategies.

Predefined exit strategies will free up injection clinics and direct treatment efforts to patients who require intensive treatment. It further gives patients a potential outlook that no lifelong treatment may be needed. In our opinion, visits every 3 months after termination of anti-VEGF therapy, combined with thorough patient counseling, are sufficient to screen for recurrences, although further studies are warranted to prove and investigate the optimal visit interval. The high percentage of patients who met exit criteria and the relatively low incidence of recurrences underlines the usefulness of an exit strategy in treat-and-extend regimens. Although the risk of a recurrence seems small, regular follow-ups are important to diagnose and treat recurrences as early as possible. Adjusting of the stability criteria should be considered in the future, especially in the matter of PED as a risk factor for disease recurrence. Patients with persistent PED may

benefit from protracted treatment at the maximal interval in a treat-and-extend regimen.

Key words: choroidal neovascularization, exit strategy, neovascular age-related macular degeneration, treat-and-extend regimen.

References

1. Friedman DS, O'Colmain BJ, Munoz B, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004;122:564–572.
2. Ho L, van Leeuwen R, de Jong P, et al. Epidemiologie der AMD. In: Altersabhängige Makuladegeneration. Berlin, Heidelberg, Germany: Springer; 2011:3–31.
3. Farinha CL, Mira F, Santos L, et al. Nutritional and lifestyle risk factors in AMD. The Coimbra Eye Study. Invest Ophthalmol Vis Sci 2015;56:3770.
4. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. Science 2005;308:419–421.
5. Zinkernagel MS, Zysset-Burri DC, Keller I, et al. Association of the intestinal microbiome with the development of neovascular age-related macular degeneration. Sci Rep 2017;7:40826.
6. Rofagha S, Bhisitkul RB, Boyer DS, et al. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). Ophthalmology 2013;120:2292–2299.
7. Maguire MG, Martin DF, Ying GS, et al. Five-year outcomes with anti–vascular endothelial growth factor treatment of neovascular age-related macular degeneration. Ophthalmology 2016;123:1751–1761.
8. Menke MN, Zinkernagel MS, Ebneter A, Wolf S. Functional and anatomical outcome of eyes with neovascular age-related macular degeneration treated with intravitreal ranibizumab following an exit strategy regimen. Br J Ophthalmol 2014;98:1197–1200.
9. Spaide R. Ranibizumab according to need: a treatment for age-related macular degeneration. Am J Ophthalmol 2007;143:679–680.
10. Wykoff CC, Croft DE, Brown DM, et al. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. Ophthalmology 2015;122:2514–2522.
11. Berg K, Hadzalic E, Gjertsen I, et al. Ranibizumab or bevacizumab for neovascular age-related macular degeneration according to the Lucentis compared to Avastin study treat-and-extend protocol: two-year results. Ophthalmology 2016;123:51–59.
12. Wickremasinghe SS, Janakan V, Sandhu SS, et al. Implication of recurrent or retained fluid on optical coherence tomography for visual acuity during active treatment of neovascular age-related macular degeneration with a treat and extend protocol. Retina 2016;36:1331–1339.
13. Kim LN, Mehta H, Barthelmes D, et al. Meta-analysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration. Retina 2016;36:1418–1431.
14. Ebneter A, Waldmeier D, Zysset-Burri DC, et al. Comparison of two individualized treatment regimens with ranibizumab for diabetic macular edema. Graefes Arch Clin Exp Ophthalmol 2016:1–7.
15. Giannakaki-Zimmermann H, Ebneter A, Munk MR, et al. Outcomes when switching from a pro re nata regimen to a treat and extend regimen using aflibercept in neovascular age-related macular degeneration. Ophthalmologica 2016;236:201–206.
16. Oubraham H, Cohen SY, Samimi S, et al. Inject and extend dosing versus dosing as needed: a comparative retrospective study of ranibizumab in exudative age-related macular degeneration. Retina 2011;31:26–30.
17. Droege KM, Muether PS, Hermann MM, et al. Adherence to ranibizumab treatment for neovascular age-related macular degeneration in real life. Graefes Arch Clin Exp Ophthalmol 2013;251:1281–1284.
18. Chin-Yee D, Eck T, Fowler S, et al. A systematic review of as needed versus treat and extend ranibizumab or bevacizumab treatment regimens for neovascular age-related macular degeneration. Br J Ophthalmol 2016;100:914–917.
19. Muether PS, Hermann MM, Dröge K, et al. Long-term stability of vascular endothelial growth factor suppression time under ranibizumab treatment in age-related macular degeneration. Am J Ophthalmol 2013;156:989–993.e982.
20. Fauser S, Schwabecker V, Muether PS. Suppression of intraocular vascular endothelial growth factor during aflibercept treatment of age-related macular degeneration. Am J Ophthalmol 2014;158:532–536.
21. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol 2008;92:667–668.
22. Gupta OP, Shienbaum G, Patel AH, et al. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration: clinical and economic impact. Ophthalmology 2010;117:2134–2140.
23. Toalster N, Russell M, Paul NA. 12-month prospective trial of inject and extend regimen for ranibizumab treatment of age-related macular degeneration. Retina 2013;33:1351–1358.
24. Essex RW, Nguyen V, Walton R, et al. Treatment patterns and visual outcomes during the maintenance phase of treat-and-extend therapy for age-related macular degeneration. Ophthalmology 2016;123:2393–2400.
25. Schmidt-Erfurth U, Waldstein SM, Deak GG, et al. Pigment epithelial detachment followed by retinal cystoid degeneration leads to vision loss in treatment of neovascular age-related macular degeneration. Ophthalmology 2015;122:822–832.
26. Waldstein SM, Simader C, Staurenghi G, et al. Morphology and visual acuity in aflibercept and ranibizumab therapy for neovascular age-related macular degeneration in the VIEW trials. Ophthalmology 2016;123:1521–1529.
27. Rayess N, Houston SKSI, Gupta OP, et al. Treatment outcomes after 3 years in neovascular age-related macular degeneration using a treat-and-extend regimen. Am J Ophthalmol 2015;159:3–8.e1.