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RETINAL DISORDERS

Comparison of two individualized treatment regimens with ranibizumab for diabetic macular edema

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Abstract
Purpose To compare outcomes between an as-needed and a treat-and-extend regimen in managing diabetic macular edema with intravitreal ranibizumab.
Methods This was a retrospective, single-centre, comparative case series on 46 treatment naive patients with diabetic macular edema. Twenty-two patients were treated following an optical coherence tomography guided treat-and-extend protocol (OCTER), and 24 patients were treated according to a visual acuity guided pro re nata regimen (VAPRN) at a tertiarry referral centre. The main outcome measures were best-corrected visual acuity, central retinal thickness, and the number of ranibizumab injections, as well as visits after 12 months of treatment.
Results After 12 months, the mean gain in best-corrected visual acuity (± standard deviation) was 8.3 ± 6.7 versus 9.3 ± 8.9 letters in the VAPRN and OCTER group, respectively ($p = 0.3$). The mean decrease in central retinal thickness was 68.1 ± 88.0 μm in the VAPRN group and 117.6 ± 114.4 μm in the OCTER group ($p = 0.2$). The mean number of ranibizumab injections was significantly different between the VAPRN (5.9 ± 1.8) and the OCTER protocol (8.9 ± 2.0) ($p < 0.001$).
Conclusion The visual acuity driven retreatment regimen resulted in a similar visual acuity outcome like optical coherence tomography guided retreatment for diabetic macular edema. Although the number of visits was similar in both groups, patients in the VAPRN group received significantly fewer intravitreal injections than patients in the OCTER group.

Keywords Anti-VEGF · Ranibizumab · Diabetic macular edema · Optical coherence tomography · Treatment regimens · Treatment burden

Introduction

Diabetic retinopathy is the most common microvascular complication of diabetes and occurs in approximately 35 % of people with diagnosed diabetes [1]. The most common cause of vision impairment in these patients is diabetic macular edema (DME), and vision loss from DME is a significant public health issue. The burden of treatment includes both direct (e.g. drug, physician remuneration) and indirect costs (e.g. stress, pain, absence from work of patient or caring relative). To minimize these expenses, it is paramount to optimize treatment protocols.

Ranibizumab is a monoclonal anti-VEGF antibody fragment [2]. Studies show superiority over laser photocoagulation, which was considered to be the gold standard before [3]. The RISE and RIDE trials demonstrated that monthly ranibizumab treatment was well tolerated and resulted in improved best-corrected visual acuity (BCVA) [4]. Nevertheless, due to potential overtreatment using monthly fixed dosing, alternative strategies were explored. The RESTORE protocol used an as-needed (PRN) approach based on BCVA stability

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[5]. Patients received intravitreal ranibizumab at monthly intervals until stable BCVA was reached, and treatment was then suspended. It was resumed if significant deterioration of BCVA was detected at monthly follow-up visits. It was shown that a visual acuity guided PRN retreatment regimen maintained the vision gained at the end of the initiation phase [6]. However, it remained unclear whether BCVA gains would have been greater if treatment had been administered monthly. Therefore, proactive treat-and-extend regimens (TER), containing components of both fixed and PRN protocols, were introduced [7]. Patients receive monthly intravitreal injections until the maximal clinical response is presumably achieved. The treatment intervals are then extended based on disease activity. The extension of intervals is tailored individually, commonly relying on optical coherence tomography (OCT) features.

Here, we compare a visual acuity based PRN protocol (VAPRN) with an OCT-guided TER (OCTER) in patients with DME, analyzing outcomes after 12 months of treatment.

Materials and methods

Study design

Retrospective, single-center, comparative case series carried out at the Department of Ophthalmology of the Bern University Hospital (Inselspital), Switzerland. As per department policy, between January 2011 and December 2012, patients with clinically significant DME were treated following a VAPRN protocol. After a transitional period, a change of policy was implemented, and all patients starting treatment after July 2013 received intravitreal injections according to an OCTER protocol. This retrospective analysis was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (KEK-Nr. 093/13). The need for written consent was waived because of the retrospective design of the project. Data were collected and managed using the REDCap electronic data management tool [8].

Patients

Forty-six eyes from 46 patients ≥ 18 years of age with either type 1 or 2 diabetes mellitus and treatment naïve center involving DME requiring treatment were included in this analysis. Key exclusion criteria were (1) previous treatment with anti-VEGF agents; (2) prior macular laser treatment; (3) prior use of intravitreal corticosteroids; (4) active periocular or ocular inflammation or infection (e.g., blepharitis, conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis); (5) uncontrolled glaucoma (e.g., intraocular pressure (IOP) ≥ 30 mmHg on medication, or deemed borderline and unsuited by the investigator); (6) neovascularizations of the anterior segment; (7) aphakia, previous vitrectomy, vitreous hemorrhage; or (8) other potentially confounding retinal pathologies. If both eyes of a patient were eligible, one eye was randomly selected.

Objectives

The primary outcomes at 12 months were mean change of BCVA and CRT from baseline in the two treatment groups (VAPRN protocol versus OCTER). Subgroup analyses were conducted based on BCVA at baseline. The secondary outcomes were the number of visits and the number of ranibizumab injections in the two treatment groups.

Assessment of outcomes

Demographic data at baseline including age at first injection, gender, glycosylated hemoglobin (HbA1c), systolic and diastolic blood pressure, past ocular history, as well as BCVA and CRT data at baseline plus during the follow-up period, were retrospectively retrieved from case notes.

Best corrected visual acuity BCVA was assessed at every visit in the OCTER group and ideally monthly (regardless of whether an injection was performed or not) in the VAPRN group using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts. Amongst both treatment groups, a subgroup analysis was performed based on baseline BCVA (good: ≥56 ETDRS letters, equivalent to 20/80 Snellen BCVA, versus poor: ≤55 ETDRS letters, respectively). This threshold was chosen because it approximately represents the cutoff for reading vision.

Optical coherence tomography OCT was performed at every visit using a spectral domain posterior segment device (Spectralis, Heidelberg Engineering, Heidelberg, Germany). The volume scan used covered 20° × 20° and comprised 49 parallel B-scans, each 120 μm apart, whereby every individual B-scan was the average of nine frames (automated real-time repetition rate = 9) composed of 512 A-scans.

Treatment

VAPRN treatment regimen Patients were treated following the BCVA based RESTORE protocol [5] with slight modifications. Briefly, they initially received at least three monthly intravitreal injections of 0.5 mg/0.05 mL ranibizumab (Lucentis®, Novartis Pharma Schweiz AG, Risch, Switzerland) until stability of BCVA was reached, e.g. no further BCVA improvement evident at the last two consecutive previous visits. Treatment was then suspended and switched to a PRN protocol with monthly visits including assessment of BCVA and OCT. Intravitreal treatment with ranibizumab was resumed if BCVA decreased by more than five ETDRS letters

within the most recent three visits and the deterioration was attributed to retinal fluid. Monthly injections were given until stable BCVA (defined as above) was reached again [5].

OCTER treatment Patients treated as per the OCT-guided Bern TER protocol received intravitreal injections of 0.5 mg/0.05 mL ranibizumab at every visit. The treatment intervals between two injections were individualized for each patient. After initiation of treatment, patients were followed and treated monthly until a stable situation of the retina on OCT was reached, e.g. absence of intra- or subretinal fluid or stable BCVA. The treatment intervals were then prolonged by 2 weeks at every visit while the situation remained stable. When recurrent intra- or subretinal fluid reappeared, the treatment interval was continuously shortened by 1 week until fluid resolution was noted on OCT. This shortened interval was then maintained for the following 6 months. Thereafter, attempts to extend the interval between visits were resumed.

Statistical analysis

The last observation carried forward approach was used to substitute missing data points. A moving average comprising 4 weeks was used to account for the different timing in the TER and PRN groups. Secondary objectives (number of injections and intervals between injections) were analyzed with an unpaired t-test. To compare the characteristics and primary outcomes between the two treatment groups, the unpaired t-test was used. A Bonferroni correction was used for testing within groups at different time points. Because the VAPRN protocol is based on monthly visits and the OCTER protocol on weekly intervals, time points had to be matched to compare between groups at the corresponding time points. Means ± standard deviations are reported in the text unless stated otherwise. Confidence intervals were two-sided and a p value of ≤ 0.05 was considered statistically significant. Data were analyzed using GraphPad Prism 5.02 (GraphPad Software) and R for Mac OS X (R 3.1.2 GUI 1.65 Mavericks build).

Results

Baseline characteristics

The outcomes of a total of 46 treatment naïve eyes treated with intravitreal ranibizumab for DME were retrospectively analyzed in this study. Twenty-four eyes of 24 patients were treated according to the VAPRN regimen, and 22 eyes from 22 patients were analyzed in the OCTER group. Demographic parameters and disease characteristics at baseline were similar for both regimens; in particular, BCVA and CRT were not statistically different between groups (Table 1).

Primary objectives: visual acuity and central retinal thickness outcomes

The mean change in BCVA from baseline over 12 months is shown in Fig. 1a. In the VAPRN group, after a rapid improvement in mean BCVA until month 3 (7.5 ± 6.3 letters), the visual average acuity gains continuously increased to 8.3 ± 6.7 letters at month 12. In the OCTER treatment group, a rapid improvement in mean BCVA was observed as of the first follow-up 4 weeks after treatment (4.9 ± 7.4 ETDRS letters), which continued up to

Table 1 Demographics and disease characteristics

Variable	VAPRN ($n = 24$)	OCTER ($n = 22$)	p Value †
Mean age ± SD (years)	63.2 ± 13.2	63.4 ± 12.0	0.84
Sex (m/f)	17/7	16/6	0.89
Mean HbA1c ± SD (%)	7.3 ± 1.0	7.6 ± 1.0	0.47
Mean SBP ± SD (mmHg)	139.3 ± 15.5	148.8 ± 21.0	0.10
Mean DBP ± SD (mmHg)	77.2 ± 7.3	82.6 ± 8.8	0.04
Mean BCVA ± SD (letters) at baseline	58.4 ± 16.6	61.6 ± 12.9	0.47
Mean BCVA ± SD (letters) at baseline in subgroup with BCVA ≥ 56 letters	72.8 ± 7.4	71.1 ± 5.6	0.34
Mean BCVA ± SD (letters) at baseline in subgroup with BCVA ≤ 55 letters	42.5 ± 8.3	47.9 ± 5.8	0.34
Mean CRT ± SD (μm) at baseline	429.6 ± 97.6	443.9 ± 122.0	0.66
Mean BCVA ± SD (letters) at baseline in subgroup with BCVA ≥ 56 letters	386.2 ± 67	408.2 ± 101	0.18
Mean BCVA ± SD (letters) at baseline in subgroup with BCVA ≤ 55 letters	473.1 ± 107	495.3 ± 137	0.44
Mean BCVA ± SD (letters) at 12 months	66.6 ± 2.9	70.9 ± 2.9	0.30
Mean CRT ± SD (μm) at 12 months	361.5 ± 22.6	326.2 ± 17.3	0.23

BCVA = visual acuity, CRT = central retinal thickness, DBP = diastolic blood pressure, SBP = systolic blood pressure, letters = EDTRS (Early Treatment Diabetic Retinopathy Study) letters, HbA1c = glycosylated hemoglobin, SD = standard deviation. † two-sided unpaired t-test

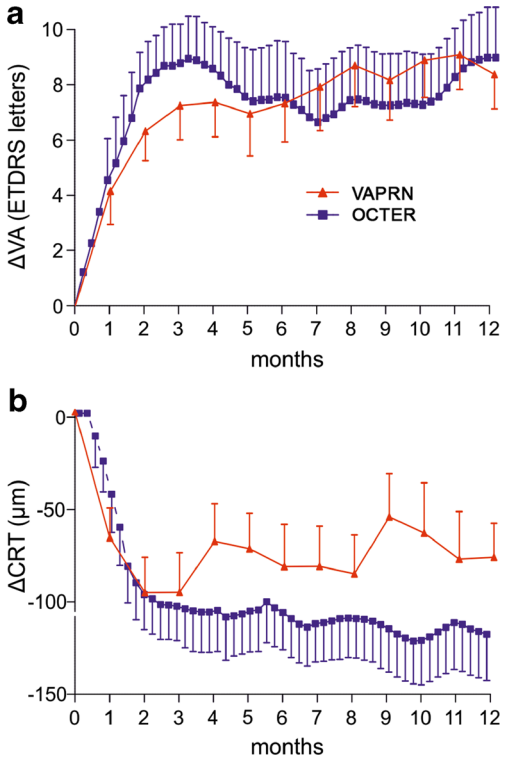

Fig. 1 Mean improvement in best-corrected visual acuity (ΔVA) in ETDRS letters (**a**) and central retinal thickness change (ΔCRT) in µm (**b**) from baseline over 12 months under treatment with ranibizumab according to the visual acuity guided as-needed regimen (VAPRN; $n = 24$) and the OCT guided treat-and-extend treatment (OCTER; $n = 22$). At none of the time points differences between treatment groups were significant. Error bars represent standard errors of the mean (only drawn in one direction)

week 11 (9.1 ± 6.8 letters). After a small dip around week 33, there was again improvement up to the last follow-up time point, at which a similar level of visual acuity was noted as at the peak around week 11. Thus, after 12 months of treatment, the mean gain in BCVA was statistically similar in both the VAPRN and OCTER treatment patients (9.0 ± 8.5 versus 9.3 ± 8.9, $p = 0.916$). In both groups, the letter gain from baseline was highly significant ($p < 0.0001$). Between the two treatment regimens, there were neither significant differences in mean BCVA letter score at 12 months ($p = 0.3$) nor at any of the previous time points assessed ($p > 0.4$).

Improvements in BCVA in both groups were paralleled by rapid reductions of CRT (Fig. 1b). From baseline to month 12, the mean CRT decreased significantly in both groups (−68.1 ± 88.0 µm, $p < 0.001$ in the VAPRN group, and −117.6 ± 114.4 µm, $p < 0.0001$ in the OCTER group, respectively). By trend, the reduction of CRT was more pronounced in the OCTER group, but the difference was not statistically significant ($p = 0.1052$). Similar to BCVA outcomes, there were neither a significant difference in mean CRT reductions between the regimens at 12 months ($p = 0.2$) nor at previous time points.

In addition, both the BCVA and CRT outcomes were scrutinized in a pre-specified subgroup analysis (Fig. 2). Initial BCVA had a significant impact on BCVA and CRT outcomes at 12 months. While patients with poor baseline BCVA (i.e. BCVA ≤ 55 ETDRS letters) experienced greater improvement in mean BCVA (12.4 ± 6.0, $p < 0.0001$ in the VAPRN group, and 12.4 ± 12.1, $p = 0.02$ in the OCTER group, respectively) and greater reduction in mean CRT (−92.4 ± 103.6 µm, $p = 0.01$, VAPRN, and −188.9 ± 131.0 µm, $p = 0.003$, OCTER), patients with better initial BCVA (i.e. BCVA ≥ 56 letters) experienced less improvement of BCVA (4.1 ± 4.5, $p = 0.01$, VAPRN, and 7.1 ± 5.2, $p < 0.001$, OCTER) and less reduction in CRT (−43.8 ± 64.5 µm, $p = 0.04$, VAPRN and −68.3 ± 70.7 µm, $p = 0.005$, OCTER) at the end of the study period. Except for two instances (BCVA at month 4 and CRT at month 10 in the subgroup with BCVA ≥ 56), neither significant differences in mean BCVA nor in mean CRT were

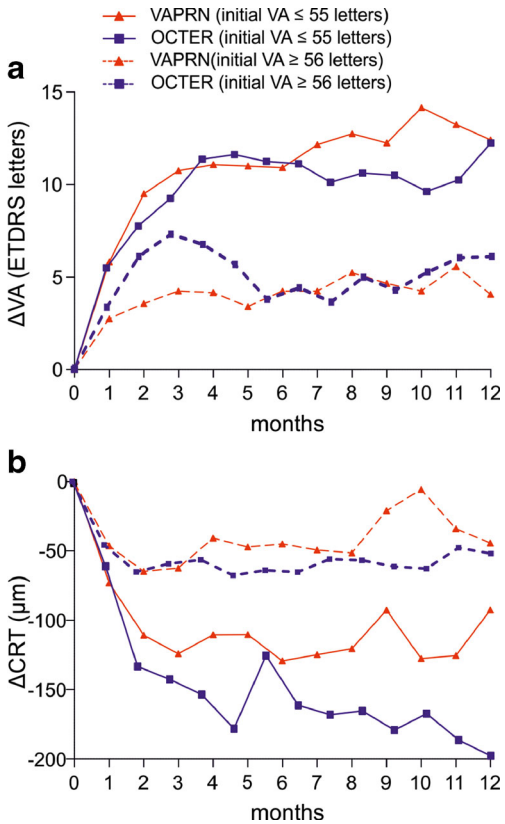

Fig. 2 Subgroup analysis according to baseline best-corrected visual acuity. Mean improvement in best-corrected visual acuity (ΔVA) in ETDRS letters (**a**) and central retinal thickness change (ΔCRT) in µm (**b**) from baseline over 12 months under treatment with ranibizumab applying a visual acuity guided as-needed (VAPRN) regimen and an OCT guided treat-and-extend (OCTER) protocol according to subgroups (initial BCVA ≤ 55 letters and initial BCVA ≥ 56 letters). VAPRN (red triangles): BCVA ≤ 55 letters: $n = 12$, BCVA ≥ 56 letters: $n = 12$; OCTER (blue squares): BCVA ≤ 55 letters: $n = 9$, BCVA ≥ 56 letters: $n = 13$. At none of the time points differences between treatment groups were significant

detected between the two treatment regimens at any of the previous time points in the subgroup analysis.

Secondary objectives: number of injections and visits

Of the 337 ranibizumab injections used during the 12-month period, 141 were administered to patients treated according to the VAPRN regimen and 196 to patients in the OCTER group. The mean number of injections per patient was significantly different between the VAPRN and OCTER group (5.9 ± 1.8 and 8.9 ± 2.0 injections, respectively, $p < 0.001$). Thus, the average treatment intensity was more than 30 % lower in the VAPRN group (Supplemental Figure).

With reference to the subgroup with poorer initial BCVA (i.e. BCVA ≤ 55 ETDRS letters), patients in the VAPRN group received significantly fewer ranibizumab injections (5.8 ± 0.6) than patients of the OCTER group (9.7 ± 0.8, $p = 0.001$). The same applies to the subgroup with better baseline BCVA (i.e. BCVA ≥ 56 letters) with 6.0 ± 0.4 and 8.4 ± 0.4 injections ($p = 0.0006$) in the VAPRN and OCTER groups, respectively.

While the number of visits for patients in the OCTER was 8.9 ± 2.0, the mean number of visits in the VAPRN group was 10.0 ± 1.5 ($p = 0.04$). The mean length of the interval between injections was significantly longer in the VAPRN than in the OCTER group (52.38 ± 45.9 and 42.5 ± 23.6 days, respectively, $p = 0.016$). The longest interval between two injections was 294 days in the VAPRN regimen and 260 days in the OCTER group.

Discussion

Intravitreal anti-VEGF therapy has become an essential treatment modality for common retinal pathologies like age-related macular degeneration, DME and retinal vein occlusion. Treatment regimens tailored to the individual patients' needs are commonly used. Whereas PRN approaches in a sense lag behind disease progression and adjust treatment intensity only once recurrences have been detected, TERs are proactive and aim at preventing relapses after reaching stability in the loading phase.

Little data on TERs for DME are currently available. The RETAIN study is the only published clinical trial that prospectively compared PRN with TER treatment for this

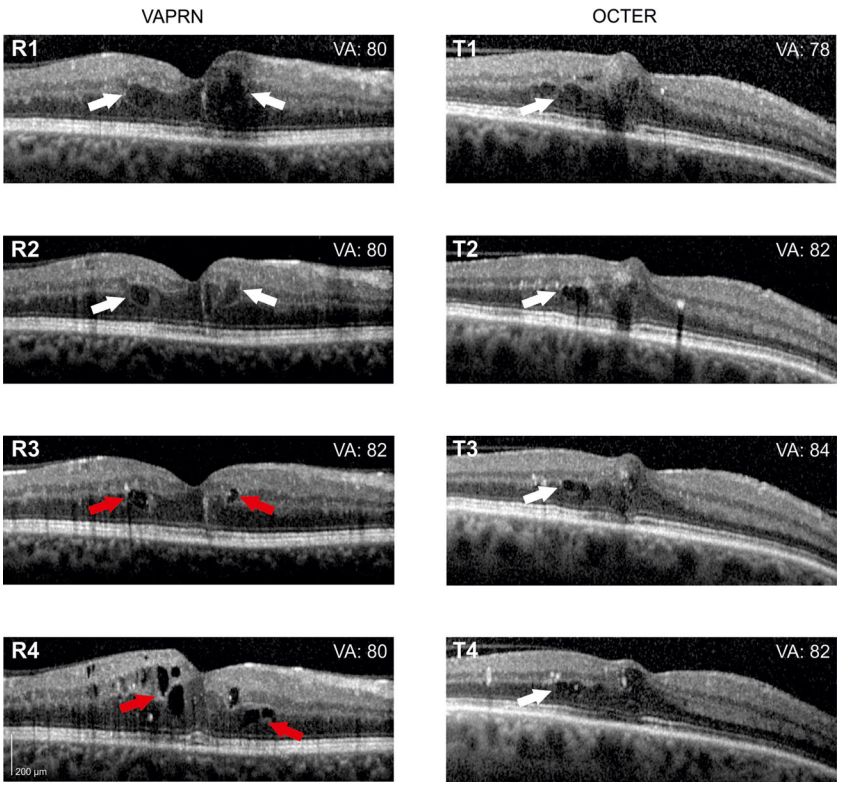

Fig. 3 Optical coherence tomography images of two representative cases from the visual acuity guided as-needed (VAPRN) regimen and the OCT guided treat-and-extend (OCTER) protocol. VA = best-corrected visual acuity (ETDRS letters). White arrow = intraretinal fluid and injection of ranibizumab on the same day, red arrow = intraretinal fluid without ranibizumab injection. VAPRN patient: Initially received three intravitreal ranibizumab injections at monthly intervals (R1 and R2 represent situation at second and third ranibizumab injection, respectively). No further injections were given at time points R3 and R4 since BCVA was stable. OCTER patient: Treated at monthly intervals because of persistent intraretinal fluid. At T4 the next visit with treatment was scheduled 5 weeks later since BCVA had been stable at the previous three visits. The injection at T4 would not have been given in the VAPRN regimen

condition. After 2 years, similar visual acuity gain was achieved in both groups with slightly fewer injections in the PRN group [9]. From a conceptual perspective, two features might explain the discrepancy in the treatment intensity between OCTER and VAPRN regimens despite similar visual outcomes. Firstly, with OCT guidance, retreatment is driven by any amount of fluid present at any location in the scan volume. Thus, the interval is shortened even if only eccentric fluid is present, which increases the number of injections without immediate BCVA benefit. This is in contrast to visual acuity guided protocols where only fluid fluctuations involving the fovea and compromising BCVA trigger treatment (Fig. 3). Secondly, whereas PRN protocols are reactive, TERs are proactive and aim at minimizing the number of relapses.

In comparison with the 1-year data from the RETAIN study [9], the visual acuity gain in our patients was 1–2 letters greater. This might be explained by the lower baseline mean BCVAs (approximately 60 letters versus 64 letters) and lesser influence of the ceiling effect, furthermore by differences in the details of the retreatment criteria. Whereas at our institution the treatment interval was shortened gradually in case of a relapse, in the RETAIN study, patients went back on three fixed monthly loading doses. Striking is the relatively low number of only 5.9 injections in our VAPRN group. In the RESTORE and the RELIGHT study [5, 10], patients with similar baseline characteristics received on average 7.0 injections in the first year. In comparison with these prospective PRN trials, it appears that the patients in our VAPRN group were undertreated due to a relatively high number of missed appointments or visits scheduled at intervals longer than the planned 4 weeks. Patients in the VAPRN group attended on average only 10 visits in 12 months instead of the expected 13. This is a major limitation of this study. To some extent, this will be reflected in the lower treatment intensity noticeable between weeks 10 and 50 (supplemental figure). We speculate that the poorer compliance in the PRN schedule might be linked to potential frustration and uncertainty inherent to such regimens. Patients are supposed to attend monthly visits but do not know beforehand whether they will be given an injection. In contrast, the treatment intervals between visits in TERs increase continuously if stability is confirmed, and patients are certain that they will get intravitreal treatment at every appointment. Lack of control and unpredictability are paramount elements in the experience of stress [11, 12]. Therefore, TERs seem more bearable for both patients and their caretakers [13]. The length of the appointments and the type of procedures during the visits are always identical and much more foreseeable.

Further limitations of this study are the retrospective design and the relatively small sample size. Moreover, while for the OCTER group analysis a week was used as the basic calculation unit, in the VAPRN protocol the basic time unit was a month. Therefore, extrapolation was necessary to define corresponding time points for comparison.

In conclusion, visual acuity led retreatment in a PRN regimen has generated functional outcomes that are comparable to results produced by OCT guidance in a TER. In the latter, the number of visits was lower and compliance better, despite higher treatment intensity. Given similar functional outcomes, this suggests that patients in the OCTER group were potentially overtreated. Further prospective studies would be needed to test this hypothesis.

Compliance with ethical standards

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Conflicts of interest Andreas Ebneter has received speaker honorarium from Bayer, educational support from Novartis, and educational support from Allergan for which he also served as an advisor.

Dominik Waldmeier and Denise C Zysset-Burri do not have any conflict of interest.

Sebastian Wolf has served as a consultant for Allergan, Bayer, Heidelberg Engineering, Novartis, Optos Inc, Zeiss and Roche, and also received grant support from Heidelberg Engineering. Furthermore, he is a board member of Euretina.

Martin Zinkernagel has served as a consultant for Allergan, Bayer, Heidelberg Engineering, and Novartis in which he also owns stock. Furthermore, he receives research grants from Bayer and Heidelberg Engineering.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the local Ethics Committee (KEK-Nr. 093/13). For this type of retrospective study formal consent is not required.

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