Spectral-Domain Optical Coherence Tomography-Driven Treat-and-Extend and Pro Re Nata Regimen in Patients with Macular Oedema due to Retinal Vein Occlusion: 24-Month Evaluation and Outcome Predictors

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Keywords

Retinal vein occlusion · Treat-and-extend regimen · Pro re nata regimen · Ranibizumab · Macular oedema

Abstract

Purpose: To analyse the efficacy and outcome predictors of ranibizumab using a spectral-domain optical coherence tomography (SD-OCT)-driven treat-and-extend regimen (TER) versus SD-OCT-driven pro re nata regimen (PRN) in patients with cystoid macular oedema (CME) due to branch or central retinal vein occlusion (BRVO, CRVO). **Methods:** Retrospective, consecutive case series. Evaluation included best corrected visual acuity (BCVA), morphological parameters on SD-OCT, and treatment frequency. **Results:** From baseline to months 12, 18, and 24, BCVA improved by 16.6 ± 13.1 , 15.5 ± 14.4 , and 16.6 ± 15.8 letters, respectively, in TER ($n = 45$), compared to 11.3 ± 17.0 , 11.0 ± 15.0 , and 10 ± 20.5 letters in PRN ($n = 31$) ($p = 0.152$, $p = 0.237$, $p = 0.172$). The mean reduction in central retinal thickness was -261 ± 189 , -272 ± 188 , and -264 ± 158 μm , respectively, in TER, compared to -130 ± 196 , -140 ± 210 , and -166 ± 207 μm in PRN ($p = 0.006$, $p = 0.017$, $p = 0.064$). 59% (53%) of TER and 22% (17%) of PRN

patients showed no intra- or subretinal fluid on SD-OCT at 12 (24) months. Using TER, the maximum recurrence-free treatment interval increased from 8.9 ± 2.3 weeks at 12 months to 9.8 ± 2.3 and 10.5 ± 2.7 weeks at 18 and 24 months, respectively. The number of injections was significantly higher in the TER than in the PRN group. **Conclusions:** In CME, due to BRVO/CRVO, TER provides better morphological outcome using more injections than PRN.

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Introduction

Along with diabetic retinopathy, retinal vein occlusion (RVO) is the second most common retinal vascular disease leading to a loss of vision [1]. For the treatment of cystoid macular oedema (CME) resulting from RVO, there are several options available like intravitreal injections of anti-vascular growth factor (anti-VEGF) substances such as ranibizumab, bevacizumab, and afliber-

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cept in addition to retinal laser photocoagulation and intraocular corticosteroids [1, 2]. The BRAVO and CRUISE studies have shown a significant improvement of best corrected visual acuity (BCVA) after treatment with intravitreal ranibizumab [3–7]. In the RETAIN study, the visual acuity (VA) effect of ranibizumab was bigger in branch retinal vein occlusion (BRVO) than in central retinal vein occlusion (CRVO) after 4 years [8]. The HORIZON study suggests that the follow-up and intravitreal injections in RVO patients should be individualized for an effective treatment and especially CRVO patients may require more frequent follow-ups than every 3 months [9]. To date, a so-called PRN scheme (pro re nata) has been applied besides monthly fixed injections, which usually starts with an initial loading dose and continues with retreatments according to various criteria. Campochiaro et al. [10] showed no difference between the patients treated with a PRN regimen and the monthly treated patients. However, this is still based on monthly examinations of the patient at the retina centre [11].

A retrospective bevacizumab study showed that by using a new treatment scheme, the treat-and-extend regimen (TER), the number of follow-up visits for patients with CME due to BRVO was considerably reduced and the treatment was individualized with favourable VA outcome [12]. For other diseases treated with intravitreal anti-VEGF drugs, such as wet age-related macular degeneration (wAMD), this is already a common treatment scheme particularly in the US [13]. TER is an individualized treatment strategy based on the clinical experience that recurrences of CME occur at regular intervals, which has at least been proven for wAMD [14]. A titration of the maximum recurrence-free treatment interval (RFTI) and finally the treatment in this time interval is aimed. The goal is the complete suppression of activity of oedema while minimizing the control and treatment costs [13]. To the best of our knowledge, besides a recent case series of 12 patients with CME due to CRVO being treated with ranibizumab using a modified TER, there are no further reports on the efficiency of a ranibizumab TER in RVO [15].

The introduction of optical coherence tomography (OCT)-based follow-up within most retina departments and recent improvements in OCT technologies offer novel insights into retinal structures with very precise imaging [1]. Central retinal thickness (CRT) was firstly used to guide (re)treatments in both, clinical trials and routine. But VA outcome seems not only to be influenced by retinal thickness [16]. Recently improved imaging quality, the follow-up mode, and eye tracking systems offer to

monitor very small changes in structure on the same spectral-domain (SD)-OCT scan at each visit and to find predictors of the anti-VEGF treatment outcome. For wAMD, already a lot of OCT biomarkers regarding the anti-VEGF treatment outcome have been evaluated [17–19]. However, for RVO, such reports are rare [1].

To the best of our knowledge, there is very limited information on the long-term efficacy of ranibizumab TER in CME due to RVO and on outcome predictors; further, there are no studies comparing TER and PRN in RVO so far. The aim of the study described herein is to analyse the long-term functional and morphological outcomes of the TER versus PRN treatment as well as to identify outcome predictors in CME secondary to RVO.

Patient and Methods

Patient Selection and Treatment Regimens

This is a retrospective, consecutive case series of patients treated at an ophthalmologic clinic in Binningen, Basel-Land, Switzerland, with at least 12-month ranibizumab PRN or TER follow-up for CME following BRVO or CRVO. In total, 76 patients were included in the analysis with consecutive recruitment within two different periods (PRN 2009–2012, TER 2012–2016), 45 in the TER and 31 in the PRN group. For patients with pretreatment, the timeframe from last treatment to study baseline had to be at least 1 month for anti-VEGF drugs and 3 months for IVTA. In TER, 45 eyes of 45 patients were reviewed during 24 months (month 12: $n = 45$, month 18: $n = 41$, month 24: $n = 32$). Reasons for drop-outs before 18/24 months of follow-up were either switching to other intravitreal agents (aflibercept $n = 5$, dexamethasone implant $n = 5$) or lost to follow-up ($n = 3$). Patients with regular TER exit (for a description of the regimen, see below) were further followed and included in the efficacy and safety analysis. In the PRN group, 7 of the total 31 patients were lost to follow-up before 24 months.

With both regimens, at baseline 0.5 mg ranibizumab (Lucentis®; Novartis AG, Basel, Switzerland) was applied, in the PRN group followed by monthly SD-OCT and clinical examinations with ranibizumab retreatment in case of intra- or subretinal fluid at SD-OCT. In the TER group, patients received ranibizumab retreatment at each subsequent visit and from week 4 onwards, the next TER interval was determined by the following criteria:

- no intra- or subretinal fluid or absolute stability of intra-/subretinal fluid as assessed by SD-OCT compared to two previous visits and the “dryest” OCT under 4-weekly treatment: extension of last interval by 2 weeks (maximum interval 12 weeks)
- new intra- or subretinal fluid or increase in previously permanently present intra- or subretinal fluid (instability): shortening of last treatment interval by 4 weeks (minimum interval 4 weeks)
- after two unsuccessful extension attempts the treatment interval remains at the last recurrence-free interval (usually the twice failed interval length minus 2 weeks)
- after three courses of the maximum interval of 12 weeks without recurrence the TER treatment was stopped (exit TER) and the patient was further followed with SD-OCT.

Intravitreal injection of 0.5 mg ranibizumab was performed according to standard procedures, including topical anaesthesia and surface disinfection with 5% povidone-iodine. RVO was diagnosed with fluorescein angiography (HRA-2; Heidelberg Engineering, Germany) using 30° setting for central fields and 55° and 102° setting, respectively, with directions of gaze for optimal view into the peripheral retina. CME was evaluated with SD-OCT (Spectralis SD-OCT; Heidelberg Engineering, Germany), using the following parameters: horizontal volume scan 19 sections, macular star 6 sections, and horizontal 6-mm scan. Both, qualitative and quantitative assessments were performed according to standard procedures. The primary outcome was the mean change in BCVA and CRT at month 12. Secondary outcomes included the mean RFTI, mean number of intravitreal injections, mean changes in BCVA and CRT during further follow-ups as well as the evaluation of outcome predictors.

The study followed the tenets of the Declaration of Helsinki, ICH-GCP and approval was received from the local ethics approval board (Ethikkommission Nordwestschweiz [EKNZ No. 2015-094]).

Data Analysis

The variables are expressed as means $\pm$ standard deviation. Shares are shown as percentages. The statistical analyses were carried out with SPSS version 24.0 for Windows (Chicago, IL, USA). For comparison of differences to baseline/previous values (dependent variables) and between different subgroups (independent variables) 2-sided *t* tests were used. A *p* value of <0.05 was considered as statistically significant.

Results

Patient Characteristics

The two groups were well balanced. The mean age was 71.7 ± 12.0 years and 72.2 ± 8.8 years in the TER and PRN groups, respectively. In TER patients, BRVO was found in 55% and CRVO including hemi-CRVO in 45%; in PRN patients, BRVO and CRVO were found in 61 and 39%, respectively. The majority (73% TER, 80% PRN) showed peripheral retinal ischaemia on fluorescein angiography at baseline; for ischaemia, ≥ 10 disc area laser photocoagulation was performed within the first 6 months. Pseudophakia was present in 24% of TER and 16% of PRN patients. In the TER group, 26% of patients had previous anti-VEGF therapy (ranibizumab) using a PRN scheme; none of the TER patients had received intraocular steroids. In the PRN group, 23% of patients had previous anti-VEGF therapy (ranibizumab, bevacizumab) or intravitreal steroids before starting the SD-OCT-driven PRN scheme. In the PRN group, the pretreated patients had received either between 2 and 5 ranibizumab/bevacizumab treatments or 1 intravitreal triamcinolone treatment; only 1 patient with longer-standing macular oedema who had multiple intravitreal triamcinolone treatments was included.

Table 1. Baseline characteristics of the patients

	TER (<i>n</i> = 45)	PRN (<i>n</i> = 31)	<i>p</i> values
Age, years	71.7 $\pm$ 12.0	72.2 $\pm$ 8.8	0.844
Gender (female)	40	45	–
CRVO	45	39	–
BRVO	55	61	–
Anti-VEGF pretreatment	26	23	–
Pseudophakia	24	16	–
Posterior vitreous detachment	80	68	–
Intraretinal deposits	93	90	–
BCVA, letters	58 $\pm$ 14	53 $\pm$ 15	0.138
CRT, μ m	550 $\pm$ 179	539 $\pm$ 177	0.793

CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion; VEGF, vascular endothelial growth factor; BCVA, best corrected visual acuity; CRT, central retinal thickness; SD, standard deviation; TER, treat-and-extend regimen; PRN, pro re nata regimen. Figures are means $\pm$ SD or percentages.

dema who had multiple intravitreal triamcinolone treatments was included. In the TER group, the pretreated patients had received between 1 and 6 ranibizumab treatments; only 2 patients with longer-standing macular oedema who had 12 ranibizumab treatments were included. For all pretreated patients, we evaluated VA before the very first treatment and compared it to the baseline VA at the start of SD-OCT-driven PRN and TER, respectively: for pretreated PRN patients, mean VA before the very first treatment was 52.8 ± 15.6 letters and mean baseline VA at the start of SD-OCT-driven PRN was 53.3 ± 15.2 letters ($p = 0.908$); for pretreated TER patients, mean VA before the very first treatment was 62.2 ± 17.5 letters and mean baseline VA at the start of TER was 60.6 ± 12.4 letters ($p = 0.789$). In the TER group, baseline posterior vitreous detachment (PVD) as evaluated by SD-OCT was found in 80% and in the PRN group in 68% of the cases. For further baseline characteristics and *p* values, see Table 1.

Visual Acuity

The mean baseline BCVA was 58.1 ± 14.2 ETDRS letters (Snellen 20/80; BRVO 60.6 ± 13.5 , CRVO 55.0 ± 14.7) in the TER group and 53.0 ± 14.9 ETDRS letters (Snellen 20/100; BRVO 53.0 ± 13.8 , CRVO 52.9 ± 17.1) in the PRN group, without a significant difference between the two groups ($p = 0.138$). The VA gain from baseline to months 12, 18, and 24 was 16.6 ± 13.1 , 15.5 ± 14.4 , and 16.6 ± 15.8 letters using TER (all $p < 0.001$) and 11.3 ± 17.0 , $11.0 \pm$

Fig. 1. Change in best corrected visual acuity (BCVA) for the treat-and-extend (TER) and pro re nata (PRN) group.

15.0, and 10 ± 20.5 letters using PRN ($p = 0.001$, $p = 0.001$, $p = 0.031$), respectively (Fig. 1). In both groups, BCVA remained stable after month 3 (Fig. 1) and the higher BCVA gains in TER compared to PRN were not significant ($p = 0.152$, $p = 0.237$, $p = 0.172$). In both groups, there was no difference in VA gain between BRVO and CRVO at 12, 18, and 24 months. At month 12, there were no TER patients losing ≥ 15 ETDRS letters; in the PRN group, 3 patients (9.7%) lost ≥ 15 ETDRS letters (2 CRVO, 1 BRVO). At month 24, in TER, 4 patients (12.5%; 2 BRVO, 2 CRVO), and in PRN, 3 patients (12.5%; 2 BRVO, 1 CRVO) had lost ≥ 15 ETDRS letters. The proportion of patients gaining ≥ 15 ETDRS letters in the TER group was 59 and 56% at 12 and 24 months, respectively; in the PRN group, it was 58 and 54%, respectively. The fluctuation of BCVA within the first 12 months (best BCVA minus worst BCVA) was significantly higher in PRN (28.5 ± 11.3) than TER (22.6 ± 12.9) ($p = 0.036$). Only in TER were greater fluctuations of BCVA within the first 12 months significantly correlated with less gain of BCVA at month 12 and 24 ($p < 0.001$) and less reduction in CRT at month 12 and 24 ($p < 0.001$).

In both groups, eyes with lower baseline BCVA (≤ 39 letters) showed higher BCVA gains at month 12 (TER 32.5 ± 14.1 , PRN 23.9 ± 20.3 letters) than those with higher baseline BCVA (≥ 60 letters) (TER 11.2 ± 8.3 , PRN 5 ± 14 letters; $p = 0.001$, $p = 0.029$). While this difference remained significant through month 24 in TER ($p = 0.001$), it showed only a trend in PRN ($p = 0.08$). Patients with lower baseline BCVA showed higher baseline CRT (TER $p < 0.001$; PRN $p = 0.014$) and greater CRT reduction at month 24 (TER $p < 0.001$; PRN $p = 0.006$). In both groups, pretreatment indicated lower VA gain at 12 months (PRN

Fig. 2. Change in central retinal thickness (CRT) for the treat-and-extend (TER) and pro re nata (PRN) group.

3.9 ± 18.1 letters; TER 8.9 ± 8.9 letters) than within all patients. Due to the low number of pretreated patients at baseline and further drop-outs within this population between 12 and 24 months, no analysis was performed for 24 months VA gain.

SD-OCT Parameters

In TER patients, mean baseline CRT was $550 \pm 179 \mu\text{m}$ (BRVO $508 \pm 151 \mu\text{m}$, CRVO $603 \pm 200 \mu\text{m}$), in PRN patients, it was $539 \pm 177 \mu\text{m}$ (BRVO $511 \pm 150 \mu\text{m}$, CRVO $583 \pm 212 \mu\text{m}$), with no significant difference between the treatment groups ($p = 0.793$). The mean reduction in CRT from baseline to months 12, 18, and 24 was -261 ± 189 , -272 ± 188 , and $-264 \pm 158 \mu\text{m}$ (all $p < 0.001$) in the

Table 2. Evaluation of baseline predictors of visual acuity (VA) gain and number of injections at 12 and 24 months in the treat-and-extend regimen (TER) and the pro re nata regimen (PRN) groups

	VA gain at 12 and 24 months					
	TER			PRN		
	group*	group**	<i>p</i> value	group*	group**	<i>p</i> value
Baseline BCVA, ≤39* vs. ≥60** letters						
12 months	32.5±14.1	11.2±8.3	0.001	23.8±20.2	5.0±14.3	0.029
24 months	32.2±10.3	10.5±14.1	0.001	26.0±23.2	1.7±17.0	0.080
Peripheral perfusion status, ischaemic* vs. non-ischaemic**						
12 months	15.4±13.1	19.5±13.2	0.365	9.4±18.1	18.8±7.6	0.065
24 months	15.6±16.4	20.0±13.5	0.484	5.0±20.8	23.3±12.1	0.019
Baseline CRT, ≤400* vs. ≥600** μm						
12 months	8.6±6.7	23.6±13.9	0.001	13.1±17.3	8.8±20.5	0.644
24 months	10.0±6.4	20.3±18.3	0.068	17.5±18.3	3.3±25.8	0.237
Baseline maximum height of largest cyst, ≥400* vs. ≤250 μm**						
12 months	20.3±16.5	12.0±9.2	0.112	5.8±20.3	10.8±16.2	0.614
24 months	18.6±19.3	11.5±12.4	0.325	-1.0±21.0	9.5±14.0	0.353
Hyperreflective foci, present* vs. non present**						
12 months	16.6±13.1	15.0±15.0	0.867	10.6±17.3	20.0±7.0	0.259
24 months	17.3±15.9	5.0±7.0	0.182	8.4±21.0	22.5±3.5	0.018
Posterior vitreous detachment, present* vs. non present**						
12 months	16.3±13.6	17.2±11.7	0.857	6.6±16.5	21.0±13.9	0.020
24 months	16.0±17.3	18.1±10.6	0.691	1.3±17.9	23.3±17.3	0.008

TER group and -130 ± 196 , -140 ± 210 , and -166 ± 207 μm ($p = 0.001$, $p = 0.004$, $p = 0.001$) in the PRN group, respectively (Fig. 2). With PRN, no OCT was performed at month 1 and only in a few cases at month 2. So, a mean CRT of all cases could not be calculated for months 1 and 2. This is important when reading Figure 2; as month 1 and 2 data are not included, the connecting line between baseline and month 3 might not reflect the initial CRT response. From month 3, the total CRT was lower in TER than in PRN during the whole follow-up ($p < 0.05$). The CRT improvement was larger in TER than in PRN at months 12, 18, and 24 ($p = 0.006$, $p = 0.017$, $p = 0.064$), with just not reaching significance at month 24. In TER, but not in PRN, there was a non-significant trend toward greater CRT reduction in CRVO than in BRVO at 12, 18, and 24 months, respectively (TER: $p = 0.065$, $p = 0.102$, $p = 0.1$; PRN: $p = 0.560$, $p = 0.942$, $p = 0.844$).

At 12 months, 59% of TER and 22% of PRN patients showed no intra- or subretinal fluid in SD-OCT ("dry OCT"); at 24 months, 53 and 17%, respectively. There was no significant difference in mean fluctuations of CRT (worst CRT minus best CRT) between TER (281 ± 186 μm) and PRN (269 ± 173 μm) within the first 12 months ($p = 0.784$). Higher CRT fluctuation in the first 12 months was correlated with lower BCVA at baseline and month 24 ($p = 0.013$, $p = 0.004$) only in the TER group, while TER patients with a thicker retina at baseline (CRT ≥ 600 μm) showed larger VA gains at months 12, 18, and 24 (23.6 ± 13.9 , 23.1 ± 13.7 , 20.3 ± 18.3 letters) than those with thinner baseline retina (CRT ≤ 400 μm) (8.6 ± 6.7 , 7.5 ± 7.5 , 10.0 ± 6.4 letters; $p = 0.001$, $p = 0.001$, $p = 0.068$). In PRN patients, no influence of baseline CRT on VA gain was detected (Table 2).

Fig. 3. Treat-and-extend group: distribution of maximum recurrence-free treatment interval (RFTI) during follow-up.

The mean maximum height of the largest intraretinal cyst at baseline was $313 \pm 145 \mu\text{m}$ in TER and $296 \pm 143 \mu\text{m}$ in PRN patients. In both groups, it showed a significant reduction to month 12 (TER $-255 \pm 160 \mu\text{m}$, $p < 0.001$; PRN $-94 \pm 208 \mu\text{m}$, $p = 0.019$), which remained significant through month 24 in TER ($p < 0.001$) but reflected only a trend in PRN ($p = 0.084$). At all follow-ups, the mean maximum height of the largest intraretinal cyst within the central 1-mm subfield was lower in TER than in PRN ($p < 0.01$) and the reduction in cyst height compared to baseline was greater in TER than PRN ($p < 0.05$). There was no correlation between the largest intraretinal cyst at baseline and BCVA at month 12 or number of injections at month 12 ($p = 0.184$, $p = 0.454$ in TER; $p = 0.101$, $p = 0.328$ in PRN, respectively).

93% of TER patients and 94% of PRN patients showed hyperreflective foci (HRF) in the central 1-mm subfield at baseline. The presence of HRF was slightly, but not significantly, reduced during follow-up. Baseline presence of HRF revealed controversial results regarding the prediction of BCVA gain during follow-up (Table 2).

Analysis of the size of the foveal avascular zone (FAZ) at fluorescein angiography (early image after complete retinal filling, 30° setting) showed a mean baseline size of $0.42 \pm 0.16 \text{ mm}^2$ for PRN and of $0.42 \pm 0.21 \text{ mm}^2$ for TER patients. During follow-up, it significantly increased (PRN $0.48 \pm 0.17 \text{ mm}^2$, $p = 0.026$; TER $0.48 \pm 0.28 \text{ mm}^2$, $p = 0.039$) but with no significant difference between the 2 groups over time ($p = 0.853$ at baseline, $p = 0.931$ at month 24, respectively). There was no correlation between change in FAZ size and VA gain.

Treatment Intervals

The mean number of injections within 12, 18, and 24 months was significantly higher in TER, with 9.6 ± 2.0 , 12.6 ± 2.5 , and 15.0 ± 3.1 injections, respectively, than in PRN, with 4.2 ± 1.8 , 5.5 ± 2.2 , and 5.8 ± 2.7 injections, respectively ($p < 0.001$). In PRN, the mean loading dose of monthly injections was 1.7 ± 0.7 . In TER, the maximum RFTI increased from 8.9 ± 2.3 (BRVO 8.8 ± 2.4 , CRVO 9.0 ± 2.3) weeks at 12 months ($p < 0.001$) to 9.8 ± 2.3 weeks at 18 months ($p < 0.001$) and to 10.6 ± 2.8 weeks at 24 months ($p < 0.001$), respectively. Figure 3 shows the distribution of maximum RFTI.

Baseline presence of peripheral ischaemia as evaluated by fluorescein angiography had no influence on the number of injections at 12 months in both groups (TER $p = 0.749$; PRN $p = 0.135$) but predicted a higher number of injections at 24 months in the PRN group (TER $p = 0.259$; PRN $p = 0.037$) (Table 2). No other predictors of the number of injections were found.

Safety

In both treatment groups, no serious adverse events were reported.

Discussion

To attempt a most individualized anti-VEGF treatment after an initiation phase, clinicians generally use either PRN or TER. While PRN has been widely used in CME due to RVO, there is limited information of TER for this indication. Our study showed a significant improvement in VA and a reduction in CRT with both regimens during the first months and stability during follow-up. Despite the real-life setting of our analysis, the VA gains in the TER group (12 months: 16.6 ± 13.1 letters) were comparable to prospective study settings such as in the CRUISE (12 months: $+13.9$ letters) and BRAVO study (12 months: $+18.3$ letters) [4, 6] and furthermore, remained stable during the second year. However, in our real-life PRN group, the VA gains (12 months: $+11.3 \pm 17.0$ letters) were somehow below the above-mentioned prospective trials, which might be explained by the less strict regimen than in a prospective trial. Furthermore, the PRN group showed a VA drop at month 3 and month 6, which might reflect the first recurrences after a mean loading dose of 1.7 injections. The difference in VA gain between the PRN and the TER group of about one line did not turn out to be significant, maybe due to the limited number of patients in each group. Unfortunately,

there are so far no other reports comparing TER and PRN in CME due to RVO.

Corresponding to the favourable VA results, CRT showed a significant decrease, which was for both of our treatment groups less than in the CRUISE and BRAVO study [4, 6], respectively, which might be due to a lower baseline CRT in our study. Nevertheless, our PRN patients showed less favourable morphological outcomes than the TER patients. The difference in CRT improvement turned out to be significant at months 12 and 18 ($p = 0.006$, $p = 0.017$) and tightly failed significance at 24 months ($p = 0.064$), while the total CRT values were significantly different during the whole follow-up. Further, a threefold higher proportion of patients showed a “dry OCT” with TER than with PRN at 12 and 24 months. The proportion of our PRN patients without visible fluid on OCT was comparable to the results of the CRYSTAL trial, a prospective PRN study in CME due to CRVO [20]. Although no comparison of our morphological TER results is possible, due to the lack of TER data in RVO, our analysis suggests better morphological outcomes than with PRN, as it has already been shown for AMD [13].

In our TER group, the number of injections within 12 months was comparable to the small CRVO study of Dirani et al. [15] using a modified TER and to the CRUISE/BRAVO trials [4, 6]. The number of injections during the second year of treatment was much higher in our study compared to HORIZON, with better VA outcome [9]. This might indicate that especially during long-term follow-up for several patients, more frequent treatment than in HORIZON might be favourable. TER might provide such a basis for an individualized long-term follow-up.

The distribution of the maximum RFTI in our TER group shows the diversity of need for anti-VEGF to keep the retina dry. Causes for the maximum RFTI increasing over time might be stabilization of the general condition (all patients were checked by general practitioners, anti-hypertensive treatment adapted if necessary). Further laser photocoagulation performed for peripheral ischaemic areas (>10 optic disc areas) could theoretically inhibit VEGF transmission by these areas. As we used wide-field imaging of the retinal periphery instead of standard 30° 7-field setting, our percentage of ischaemic labelled RVOs was rather high. Singer et al. [21] showed that the baseline amount of peripheral non-perfusion correlates with both the baseline retinal thickness and the magnitude of reduction in oedema with anti-VEGF treatment. This might implicate that especially these patients with big peripheral non-perfusion areas have high VEGF levels, which

drive an extensive baseline macular oedema and show (due to the higher baseline CRT) a good treatment response. Maybe due to the short follow-up period of 6 months, the low number of retreatments, and rather weak retreatment criteria, Singer et al. [21] failed to show a correlation of ischaemic index and treatment frequency [20]. In our study, in TER there was no significant difference between the ischaemic and non-ischaemic patients with respect to VA gain and number of injections at 12 and 24 months while PRN patients showed both, a lower VA gain in ischaemic eyes (12 and 24 months) and a higher need for anti-VEGF injections (trend at 12 months, significance at 24 months). Possible reasons for the lack of correlations with TER could be the low number of non-ischaemic eyes, the early photocoagulation treatment of big ischaemic areas and the strong suppression of VEGF by regular injections within TER. Within a less intensive anti-VEGF treatment such as PRN, this seems to play a more important role.

Known predictive factors for visual outcome are VA and CRT at baseline. In the CRYSTAL and BRIGHTER trials (PRN), mean VA change from baseline at month 6 and 12 was higher in patients with a lower baseline BCVA compared with those with a higher baseline BCVA [20, 22]. Our study showed a similar correlation: low baseline VA resulted in higher VA gain during 12 months compared to high VA. Furthermore, in the TER group, eyes with less severe macular oedema experienced a lower gain in BCVA during 12 months than these with severe macular oedema.

Beside baseline VA and CRT, our study evaluated further outcome predictors, which have not been evaluated so far in anti-VEGF TER. Recently, HRF attracted the attention of several authors as an SD-OCT finding in retinal vascular diseases [23] and AMD [17–19]. In our study, the presence of HRF was slightly, but not significantly, reduced during follow-up. Probably due to the unequal distribution of HRF and the limited number of patients in total, there was no significant predictive value of HRF regarding VA gain and number of injections.

For AMD, PVD has recently been described as a predictive factor regarding VA outcome dependent on treatment frequency. In an EXCITE post hoc analysis, patients without PVD at baseline demonstrated higher BCVA gains with frequent treatment while patients with PVD had similar visual outcomes regardless of treatment frequency [24]. Our results with higher VA gains in eyes without PVD compared to PVD eyes in the PRN group might also support a role of PVD in ranibizumab-treated CME due to RVO. However, due to the low number of

non-PVD eyes, especially in the TER group, no direct conclusion can be drawn.

The FAZ size was similar in both groups and increased significantly over time, showing no correlation with VA at month 24 – maybe due to the overall small FAZ sizes and the patient selection (eyes with baseline VA <35 letters and relevant baseline macular ischaemia were not treated following PRN or TER for at least 12 months and therefore not included in this analysis). A further reason could be the limited follow-up period of 2 years.

Limitations of our study are its retrospective nature and the limited number of patients. No severe safety issues were identified while using ranibizumab in these settings. In conclusion, the individualized treatment schemata TER and PRN can significantly improve VA and OCT morphology in a real-life setting. TER provides better morphological outcome using more injections than PRN. Baseline BCVA was found to be a VA outcome predicting factor in both treatment groups while further outcome predictors differed between treatment groups. For further evaluations of predicting factors, larger settings are needed.

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Author Contributions

All authors participated in the interpretation of data, drafting or critical revision of the manuscript and approval of the final version of the manuscript, and agreed with the decision to submit the manuscript for publication.

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