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Comparison of Strategies of Treatment with Ranibizumab in Newly-Diagnosed Cases of Neovascular Age-Related Macular Degeneration

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Abstract

Purpose: In several case-studies improved outcomes have been reported after switching from a *pro-re-nata* (PRN)- to a treat-and-extend (T&E)-based therapeutic approach in cases of neovascular age-related macular degeneration (nAMD). We therefore wished to compare the effects of instigating 2 different protocols in newly-diagnosed nAMD undergoing treatment with Ranibizumab.
Methods: The outcomes of a PRN- and a T&E-based regime were retrospectively compared in treatment-naïve eyes under therapy with Ranibizumab for minimally 12 months in a routine clinical setting. The primary outcome measures included the proportion of the eyes with intraretinal fluid in OCT and visual stability after the initial drug-loading phase.
Results: The comparative case-series included 107 eyes (PRN: 68; T&E: 39). During the 2-year follow-up period, a similar number of clinical examinations were performed in the 2 groups (PRN: 14.0 ± 6.2; T&E 13.4 ± 4.4; $P = 0.97$), whereas the number of injections that were administered differed for the first (PRN: 5.5 ± 2.0 vs. T&E 6.8 ± 2.4; $P = 0.008$) and the second year (PRN: 1.9 ± 2.0 vs. T&E 3.8 ± 2.3; $P = 0.002$). The proportion of eyes with intraretinal fluid after the initial drug-loading phase remained stable (PRN: from 33.8% to 36.4%; T&E: from 25.6% to 29.0%); so, too, did the central retinal thickness and the visual acuity.
Conclusion: Despite a limited sample size, this retrospective analysis revealed the anatomical and the functional improvements during the 2-year follow-up period to be not roughly different for the 2 strategies. However, when the PRN-approach is instigated, the risk of under-treatment due to lapses in visits or to over-extensions in the intervals between treatments may be underestimated.

Keywords: wet age-related macular degeneration, intravitreal injections, Ranibizumab, *pro-re-nata*, PRN, treat-and-extend

Introduction

Since the drug's introduction on the market in 2007, the mode of treating wet age-related macular degeneration (AMD) with Ranibizumab has undergone changes that reflect clinical experience with the agent, with injections at fixed monthly intervals giving way to a *pro-re-nata* (PRN)-based approach.[1] During the ensuing years, the long-term outcomes that were achieved using a PRN-strategy were revealed to be inferior to those that were elicited by the administration of injections at fixed monthly intervals,[2–4] and under-treatment may have been a contributory factor.[5] The findings of the Sustain study,[6,7] the 2-year data of the CATT- and the IVAN-trials,[2,3] and the long-term results of the Seven-Up survey,[4,8] have placed physicians in the uncomfortable position of having to choose between the loss of vision that is an inherent risk of under-treatment[5] according to a PRN-regime and the induction or enhancement of geographic atrophy that is associated with monthly injections.[8–10]

The still now frequently instigated PRN-strategy advocates monthly injections until the lesion has stabilized [absence of intraretinal fluid, no or stable levels of subretinal fluid, and detachment of the retinal pigmented epithelium (RPE) over 3 consecutive injection intervals]. The therapy is then interrupted, with monthly-to-bimonthly controls, until lesion activity recurs (new intra- or subretinal fluid or additional RPE-detachment), when the same pattern of treatment is re-initiated. Using this protocol, a decline in visual

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acuity may be detected already within 2 years, which is not the case when continuous monthly strategy is pursued.[2,3] Even in the setting of a clinical study, this decline will lead to a complete loss of the visual gain within a few years.[4] In routine clinical practice this point may be achieved as early as 2 years after the initiation of treatment, depending on the number of injections and the number of follow-up visits.[11] Since treatment on a monthly basis is an inacceptable burden for most patients under study as well as under clinical routine conditions (more than 50% of the participants were lost to follow-up after the first year in the AURA-[11] and in the CATT-trials[2]), this strategy was replaced by a treat-and-extend (T&E)-based one,[12] in which the number of injections that are administered after a drug-loading phase involving 3 injections is adapted to the individual needs of the patient, thereby reducing the clinical burden and increasing the chance of an improvement in the long-term visual outcome.[13–16]

According to a recently-published meta-analysis of 1,046 peer-reviewed articles that reported on the outcomes of treatment with Ranibizumab or Bevacizumab in cases of neovascular age-related macular degeneration (nAMD) after minimally 12 months until the end of 2013, the T&E-regime was adopted in only 8 of the studies and the PRN-strategy in 62. After 1 year of treatment, an average visual gain of 5.4 ETDRS-letters was achieved in the PRN-group after 5.6 injections, compared with 10.4 ETDRS-letters in response to 8.1 injections in the T&E-group. Interestingly, at the end of the first year, the difference between the 2 groups in central retinal thickness (CRT; PRN: −100 µm; T&E: −88 µm) did not correspond to the remarkable one in visual gain, which may reflect sampling errors.[17]

Consequently, more long-term data, with follow-up periods exceeding 12 months, are needed to guide the mode of treatment in routine clinical practice. With this aim in view, we compared the anatomical and the functional outcomes of treatment with Ranibizumab over a period of 2 years in a series of treatment-naïve eyes with nAMD before (2009–2012) and after (2013–2015) the switch from a PRN- to a T&E-based regime.

Methods

Patients with newly-diagnosed nAMD who were undergoing treatment in the macula clinic of the Berner Augenklinik am Lindenhofspital were included in this retrospective study if the following criteria were fulfilled: (1) need for intravitreal injections of Ranibizumab due to choroidal neovascularization (CNV)-activity, as by the optical coherence tomography (OCT)-revealed presence of intra- and subretinal fluid; (2) initiation of treatment between 2009 and 2015 with minimally 3 intravitreal injections of Ranibizumab; (3) a follow-up period of minimally 12 months after the onset of therapy. Eyes that satisfied the inclusion criteria were subdivided according to the period during which the therapy had been initiated: 2009–2012 (group 1) and 2013–2015 (group 2). The follow-up period for the eyes in group 1 had to be terminated before the end of March 2013 owing to the change in the treatment regime after this time. The follow-up period in group 2 ran until the end of September 2016.

Group-1 eyes that were undergoing treatment during the second phase of the study were excluded from the group-2 analysis ($n = 25$), even though an independent comparison with treatment-naïve group-2 eyes had revealed no differences between the 2 subdivisions after the initial drug-loading phase.

Lesion stability was defined as the absence of intraretinal fluid, no or stable levels of subretinal fluid, and RPE-detachment over 3 consecutive injection intervals. During the break in therapy, the eyes were monitored every 4–8 weeks according to the availability of the patients.

After the initial drug-loading phase and the completion of the series of monthly injections that led to lesion stability, the PRN-regime was instigated on a monthly-to-bi-monthly basis. The re-initiation of treatment was guided by spectral domain OCT-based anatomical criteria. The aim was to regain lesion stability at each recurrence, but without the re-initiation of a new drug-loading phase. According to the T&E-approach, a 2-week extension of the visit and the treatment intervals was permitted after each consultation, if the lesion was found to be stable, until maximally 14 weeks. The patients were treated at each visit, and an interruption of the therapy was offered if the lesion was stable for more than 6 months with injection intervals 12–14 weeks.

The study fully complied with the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the University of Bern (reference KEK No. 099/15). Before inclusion in the study, the patients gave their informed consent for the use of their coded data.

Exclusion criteria

Sixty-five eyes were excluded from the study. The exclusion criteria included: (1) follow-up period of <12 months; (2) the existence of an underlying disease that could potentially interfere with the clinical outcome, namely, an active vascular disorder (any stage of active diabetic retinopathy) or an inflammatory ocular one (uveitis); (3) CNV of possibly another aetiology; (4) non-compliance with scheduled visits; (5) pre-treatment with intravitreal steroids up to 6 months before the switch in therapy.

Data acquisition

Data appertaining to the patients were extracted from their electronic records. They included Snellen best-corrected visual acuity, which was converted to the corresponding ETDRS-letter score,[18] intraocular pressure and functionally-relevant anatomical (OCT-based) findings. Both eyes were included if the patient was undergoing bilateral treatment. The CRT was measured using a horizontal line algorithm of 6 mm (Spectralis™; Heidelberg Instruments, Heidelberg, Germany). The investigator's decision as to whether the macula was dry (absence of fluid) or not (any fluid in a central zone that spanned 2 mm) was based on the use of the same algorithm.

The CRT-measurements were executed by a trained independent reader (H.M.R.), who was blinded to the group affiliations of the patients. The measurements were made on a micrometre scale from the inner retinal surface to Bruch's membrane if this was visible; if it was obscured by the subretinal hyper-reflective mass that represented the fibrovascular complex, then its position was estimated.

The data were collected from the time of the diagnosis to that of the final follow-up visit before the data lock on September 30, 2016. They were recorded at the time of the diagnosis before the onset of treatment with Ranibizumab (T0), after 3 consecutive intravitreal injections of Ranibizumab

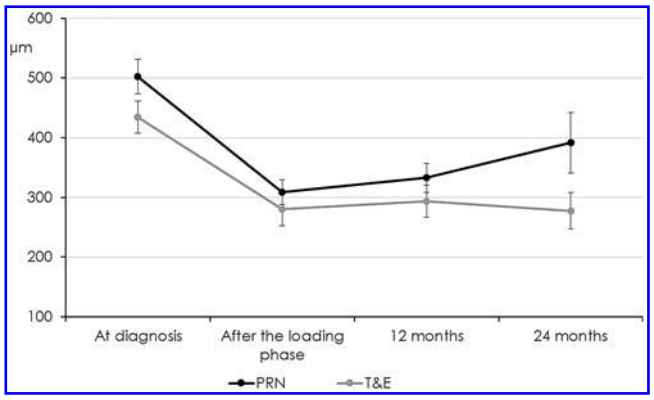

FIG. 1. Central retinal thickness (OCT-based measurements). Sample size (*n*): at diagnosis (PRN = 68, T&E = 39); after loading phase (PRN = 67, T&E = 39); 12 months (PRN = 65, T&E = 39); 24 months (PRN = 21, T&E = 31). PRN, *pro-re-nata*; T&E, treat-and-extend; OCT, optical coherence tomography.

following the initial drug-loading phase (T1), after 12 months (T2), and after 24 months (T3).

Statistical workup of data

On the basis of the assumption that the groups were independent and behaved differently in their temporal response to therapy, and considering the circumstance that the data were not normally distributed, a series of non-parametric tests were performed. To test for the significance of differences in the ETDRS-letter score, Wilcoxon's signed-rank test was conducted for each group separately. Since multiple comparisons increase the risk of introducing a type 1-error, the significance level was adjusted using Bonferroni's correction to $P \leq 0.008$. To ascertain whether inter-groups differences existed in the ETDRS-letter scores, in the annual number of intravitreal injections and in the time that elapsed before re-treatment, the Mann-Whitney U-test was applied.

Qualitative data appertaining the patients in each group were compared using separate Pearson chi-squared-tests at each time point. All statistical analyses were performed using the SPSS software package V.23 (SPSS, Inc., Chicago, IL), with the level of significance being set at $P < 0.05$. Unless otherwise stated, the data are represented as mean values together with the standard deviation.

Results

A total of 107 eyes in 96 patients satisfied the inclusion criteria [PRN (group 1): 68 eyes, 61 patients; T&E (group 2): 39 eyes, 35 patients]. At the time of the diagnosis, the patients in the 2 groups were of comparable age [PRN: 80.2 ± 7.3 (62.2–94.1) years; T&E: 82.6 ± 6.3 (70.9–95.2) years; $P = 0.27$], gender (PRN: 60.3% females; T&E: 64.1% females; chi-squared test: $P = 0.84$) and lenticular status (PRN 57.4% pseudophakic; T&E 41% pseudophakic; chi-squared test: $P = 0.13$). After the onset of treatment, the follow-up times for the 2 groups differed from each other [PRN: 16.9 ± 5.6 (11.4–25.9) months; T&E: 21.8 ± 5.0 (10.6–26.9); $P = 0.0005$]. This difference is explained by the fact that during the observation period of this study, several patients were switched from a PRN- to a T&E protocol so that their data after switch had to be excluded from further analysis.

Although the total number of visits that were made during the 2-year follow-up period was comparable in the 2 groups (PRN: 14.0 ± 6.2 visits; T&E 13.4 ± 4.4 visits; $P = 0.97$), more were scheduled for patients in the PRN-category during the second year [PRN: 5.7 ± 3.5 (1–18) visits; T&E: 4.0 ± 1.5 (2–8) visits; $P = 0.023$]. However, the significance of the difference was lost after applying Bonferroni's correction ($P > 0.008$). More injections of Ranibizumab were administered to patients in the T&E- than to those in the PRN-group during both the first year [PRN: 5.5 ± 2.0 (3–10) vs. T&E: 6.8 ± 2.4 (3–12) injections; $P = 0.008$] and the second [PRN: 1.9 ± 2.0 (0–7) vs. T&E 3.8 ± 2.3 (0–7) injections; $P = 0.002$] and thus, not surprisingly, from the time of diagnosis up until the 2-year juncture [PRN 7.3 ± 3.3 (3–15) vs. T&E 10.1 ± 3.0 (3–14) injections; $P = 0.002$]. These differences remained significant even after the application of Bonferroni's correction ($P \leq 0.008$).

In both of the groups, the CRT decreased significantly after the 3 loading injections of Ranibizumab had been administered, and thereafter remained stable (Fig. 1 and Table 1) This parameter tended to be lower in the T&E- than

Table 1. Change in Central Retinal Thickness (µm)

	T0–T1		*T0–T2*		*T0–T3*		*T1–T2*		*T2–T3*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
PRN	−197.8, $z = -6.72$, $P = 0.0005$	171.3	−185.72, $z = -5.98$, $P = 0.0005$	196.86	−133.35, $z = -2.20$, $P = 0.028$	238.03	21.2, $z = -0.23$, $P = 0.82$	138.7	−21.2, $z = -0.07$, $P = 0.95$	215.4
T&E	−154.4, $z = -4.90$, $P = 0.0005$	151.9	−141.08, $z = -4.86$, $P = 0.0005$	127.79	−145.84, $z = -4.30$, $P = 0.0005$	162.81	13.3, $z = 0.54$, $P = 0.59$	86.3	−20.2, $z = -0.13$, $P = 0.89$	92.7
Mann-Whitney U test	$P = 0.35$		$P = 0.34$		$P = 0.73$		$P = 0.46$		$P = 0.91$	

To analyze if the change of CRT between time points changed significantly within 1 group, a series of Wilcoxon signed-rank tests was performed (*upper* part of the table). To analyze if there were significant differences between PRN and T&E, the Mann-Whitney U test was applied (*lower* part of the table).

CRT, central retinal thickness; PRN, *pro-re-nata*; SD, standard deviation; T0, time of diagnosis before first Ranibizumab treatment initiation; T1, after the Ranibizumab loading phase; T2, after 12 months; T3, after 24 months; T&E, treat-and-extend.

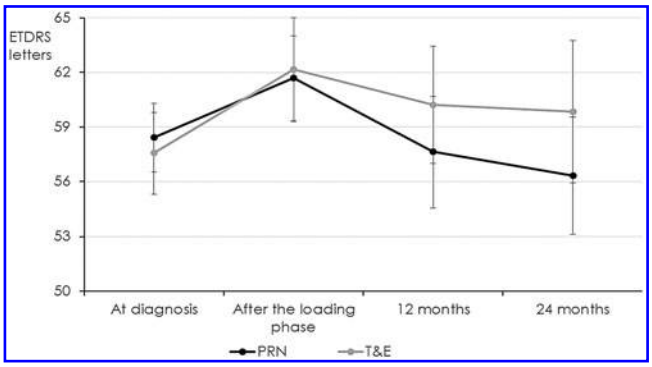

FIG. 2. Best-corrected visual acuity (ETDRS letter scores). Sample size (*n*): at diagnosis (PRN = 68, T&E = 39); after loading phase (PRN = 67, T&E = 38); 12 months (PRN = 68, T&E = 39); 24 months (PRN = 23, T&E = 30).

in the PRN-group ($P = 0.054$). At the 1- and 2-year junctures, the standard deviation was 2-fold higher in the PRN- than in the T&E-group, which suggests that the CRT was more stable in patients of the latter class.

The temporal evolution of visual acuity is depicted in Fig. 2. In both of the groups, and according to expectation, this parameter improved after the onset of treatment (T0) up until the end of the drug-loading phase (T1). Thereafter, a visual decline of 5 letters was observed in both of the groups until the end of the 2-year observation period (Table 2), which did not, however, attain statistical significance, either within or between the 2 categories. This finding may reflect the circumstance that due to the retrospective nature of this study the consultations at the 2-year juncture were not pre-scheduled end-of-study ones but rather re-treatment visits to handle recurrences in some of the PRN-patients; as such, the measurement was not representative of the visual potential at the time.

Discussion

In the present comparison of Ranibizumab-treatment strategies, only treatment-naïve eyes that had been handled according to the same regime for 12–24 months, but not thereafter, were included, to eliminate sampling errors. During the 2 years that followed the drug-loading phase, the values for the anatomical (CRT) and functional parameters (visual acuity) did not differ significantly between the 2 groups, although trends were apparent in the temporal courses. The functional outcomes for the PRN-group accorded with existing data, whereas those for the T&E-category lay well below the expectations.[17]

The absence of detectable differences in our study may reflect the smallness of the sample size, which was a consequence of the restrictive inclusion criteria and of the confinement of the follow-up period to 24 months. Consistent with this argument is the finding that the reductions in CRT—by 133 and 146 μm in the PRN- and the T&E-group, respectively (Table 1)—were at least as good as those that were reported in the aforementioned study,[17] using similar numbers of injections (PRN: 5.6 injections; T&E: 8.1 injections[17] vs. PRN: 5.5 injections; T&E: 6.8 injections in our case series).

Although the anatomical responses do not seemingly support the argument, the number of visits and injections that took place during the second year did not suffice for an optimization of the functional outcomes. In actual life, patient compliance and co-morbidity may counteract optimal treatment in the long run.

We also analyzed the data of cases in which a switch in the therapeutic strategy from the PRN- to the T&E-regime was made (data not shown). These patients were excluded from the study on the grounds that the visual stability may have been linked with the duration of the follow-up period.[2,4] Notwithstanding this potential influence, the visual stability after the initial drug-loading phase was similar in these and the treatment-naïve eyes. This finding is not in accordance with those of a recently published longitudinal study, in which the visual gain after a switch in the therapeutic regime was evaluated.[19] An average visual gain of 5 letters was reported, which is a greater improvement than would have been expected for a mean of 17 months (range 3–55) after the attainment of what had been deemed to be a stable situation under the PRN-regime. Not surprisingly, significantly better outcomes were documented for the subgroup of patients in which the switch in the therapeutic strategy had been effected after fewer than 12 months of treatment under the PRN-regime than for that in which it had been made after a year or more.[19]

Table 2. Change in Best-Corrected Visual Acuity (ETDRS Letters)

	T0–T1		*T0–T2*		*T0–T3*		*T1–T2*		*T2–T3*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
PRN	4.5, $z = 3.20$, $P = 0.001$	12.5	0.66, $z = 1.52$, $P = 0.13$	19.53	−3.67, $z = -0.68$, $P = 0.50$	14.97	−3.5, $z = -0.84$, $P = 0.40$	16.4	−2.5, $z = -0.54$, $P = 0.59$	14.2
T&E	4.3, $z = 2.69$, $P = 0.007$	11.9	2.65, $z = 1.18$, $P = 0.24$	16.60	1.43, $z = 0.95$, $P = 0.34$	17.95	−2.6, $z = -0.72$, $P = 0.47$	12.7	−4.0, $z = -1.90$, $P = 0.06$	10.5
Mann-Whitney U test	$P = 0.93$		$P = 0.06$		$P = 0.85$		$P = 0.85$		$P = 0.61$	

To analyze if the change of ETDRS letters between time points changed significantly within 1 group, a series of Wilcoxon signed-rank tests was performed (*upper* part of the table). To analyze if there was a significant difference between PRN and T&E, the Mann-Whitney U test was applied (*lower* part of the table).

T0, time of diagnosis before Ranibizumab treatment initiation; T1, after the Ranibizumab loading phase; T2, after 12 months; T3, after 24 months.

The recurrence of disease activity at the time of switch (as in our patients) and the instigation of a new drug-loading phase at this juncture (which was not undertaken in our patients) may have had a considerable impact on the outcomes. In the CATT-trial, substantial lesion growth was observed in both PRN-arms over a period of 2 years. Since this parameter is arguably the strongest predictor of the long-term outcome of treatment, a visual gain was to be expected in the patients of the aforementioned study,[19] who underwent an intense course of treatment under the T&E-regime, with an initial injection interval of 1 month. At the time when the switch in the therapeutic regime was implemented, the highly variable and thus unpredictable status of the eyes precluded a normalization of the number of visits or injections or a prediction of the treatment demand under the PRN-regime.[20]

Consequently, caution must be exercised in interpreting the findings of the comparison between the 2 approaches. It was with a view to facilitating a direct comparison between the 2 protocols that only treatment-naïve eyes were included in our analysis. However, in practice, adherence to 1 or the other protocol was not always strict, especially in the instance of the T&E-approach. This reality underlines the difficulties that may be encountered in implementing a new treatment strategy in routine clinical practice, which in our experience can take more than a year.

In another retrospective study, involving 90 patients, the gain in visual acuity was greater in the T&E- than in the PRN-group (10.8 letters vs. 2.8 letters, $P=0.04$).[15] The individuals in the former category performed better and those in the latter worse that in our analysis. In the aforementioned study,[15] no differences in the number of visits were reported between the 2 groups. However, the number of injections that were administered was higher in the T&E- than in the PRN-group, which accords with our findings (with 1 visit fewer in each category). This former study was undertaken 5 years ago, and it is thus somewhat surprising that it did not prompt the performance of more comparative analyses appertaining to the topic than we have identified.

In 1 recently-published meta-analysis,[17] no clear benefit could be attributed to either of the 2 treatment regimes, although a trend in favour of the T&E-approach was apparent during the first year of therapy, which was the chosen end-point for the evaluation. This conclusion accords with our own views. Anatomical parameters, such as a change in lesion size (which can be determined with accuracy only if angiography is regularly performed), CRT or the proportion of eyes intraretinal fluid, may be more predictive of long-term visual stability than are functional ones.[21] As with visual acuity, no differences in either the CRT or the proportion of eyes that harboured any fluid *per se* (Fig. 3A) or intraretinal fluid specifically (Fig. 3B) were observed between the 2 groups. With respect to CRT, our findings accord with those of the meta-analysis.[17]

Among the limitations of our study, patient compliance with the scheduled visits and with the treatments programme are worthy of mention. In our study, the number of visits that were scheduled for the first year in the PRN-group of patients lay below the predicted estimates, since the interval between the controls was extended by up to 2 months in the event of lesion stability. In the T&E-group, the number of visits that were scheduled for the first year corresponded pretty well with the predicted estimates. Hence, lapses in the treatment programme were not accountable for the absence

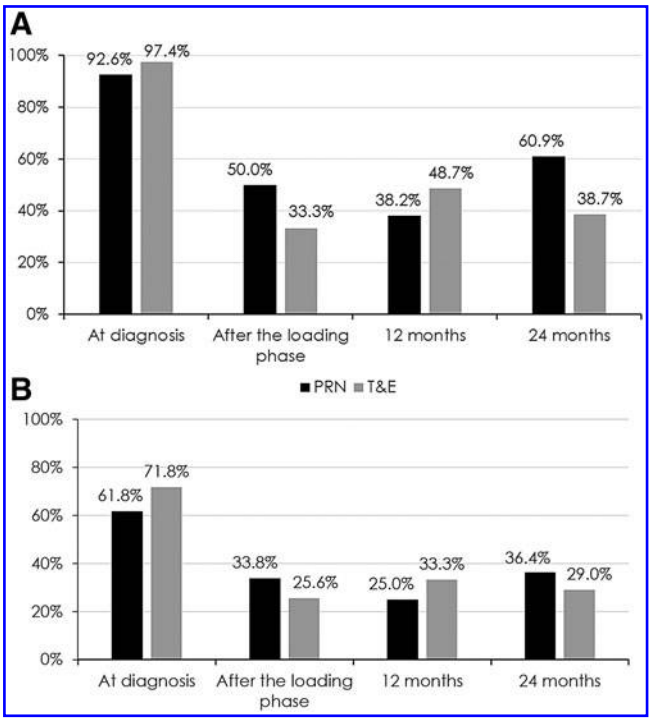

FIG. 3. **(A)** Presence of any fluid (revealed by OCT). **(B)** Presence of intraretinal fluid (revealed by OCT).

of an expected difference in the outcomes between the 2 groups. Lapses in compliance with the scheduled visits and interruptions in the treatment program represent problems that are typically encountered in the follow-up of patients in a real-life situation, although this confounder probably impacts both groups equally.[2,3,11] This circumstance may explain why the outcomes in the T&E-arm of the TREX-study[22] differed so greatly from those in our own study.

Another limitation of our study was the smallness of the sample size, which was a consequence of the restrictive inclusion criteria. Notably, patients in whom a switch in the Ranibizumab-treatment regime had been effected and those in whom the therapeutic agent had been changed were excluded from the analysis. These stipulations which, on the one hand, carried the drawback of a reduction in sample size, on the other conferred the advantage of streamlining the analysis. Moreover, the follow-up period of 2 years was longer than has hitherto been the case in comparative studies of a similar nature. Given the limitation that was imposed by the smallness of the sample size, it was not our aim to demonstrate the superiority of the one or the other regime in clinical practice. Rather, we wished to bolster the pool of available clinical data appertaining to the 2 protocols and to demonstrate the need for undertaking direct comparative analyses.

This information is required to ascertain whether the long-term outcomes that are achievable under the T&E-regime bare out the promising findings of the short-term analyses. Currently, the long-term outcomes are no more predictable than they were at the time when the PRN-regime was first introduced in 2006. The differences in the anatomical and the functional outcomes that were achieved under the 2 different treatment regimes were surprisingly small, and we thus remain critical of any strategy whose advantages respecting both the anatomical and the functional parameters have not been confirmed in a prospective long-term setting.

In conclusion, bearing in mind the limitations that were intrinsic to the retrospective nature of the analysis and the limited sample size, our findings indicate that anatomical and functional improvements can be achieved using both strategies. In a routine clinical setting, the risk of undertreatment due to non-compliance with the scheduled visits and the consequent prolongations of the intervals between injections should not be underestimated.

Acknowledgment

Part of the data that are presented herein have also been used in another publication.

Author Disclosure Statement

J.G.G. advices several pharmaceutical companies (Alcon, Allergan, Bayer, Novartis) and participates in a number of pharma-sponsored international multicenter clinical studies (Novartis, Bayer) in the fields of AMD and diabetic retinopathy. These activities had no bearing on the study that gave rise to the submitted article, for which he received neither direct nor indirect financial support; nor has he conflicts of interest with any of the presented data. None of the other authors have declarations of potential conflicts of interest.

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