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RETINAL DISORDERS

Retreatment by series of three intravitreal injections of ranibizumab in neovascular age-related macular degeneration: long-term outcomes

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Abstract
Background The purpose of this study was to analyze the results of a retreatment regimen using a series of three monthly intravitreal ranibizumab injections (IVR), instead of one injection, and to determine if this treatment scheme can safely reduce the number of injections and the number of visits compared to the widely used PrONTO study retreatment protocol.
Methods >Sixty-six eyes of 60 patients with exudative age-related macular degeneration (AMD) were included. The mean follow-up period was 27 months (range, 11–48 months). The mean age of the patients was 79 years (range, 65–93 years). All patients received three initial IVRs, and were retreated with a new series of three monthly IVRs when needed. The retreatment criteria were: visual loss of ≥5 ETDRS letters and/or signs of retinal exudation on OCT, new macular hemorrhage, expansion of new vessels. Follow-up visits were conducted 1 month after the last IVR of each series, and renewed on a monthly basis when no retreatment was required. Each visit included a comprehensive ophthalmological examination with BCVA measurement and OCT examination.
Results Mean VA did not improve during follow-up (53.18 letters at the initial visit versus 54.18 at the last visit, $p>0.05$). However, VA stabilized or improved in 66.6 % of the eyes. A gain of ≥15 letters was observed in 28.8 % of eyes. On average, over 2 years, the number of IVRs was five per year, and the number of follow-up visits was four per year.
Conclusion Even if no gain in VA is observed after 2 years, this treatment regimen reduces the number of IVRs and control visits. The proportion of patients with a VA gain of three lines or more was smaller than the one reported in the original PrONTO study, but higher than the rates reported in other studies implementing the PrONTO recommendations in everyday practice. The benefit of the three IVR retreatment scheme should be prospectively studied and compared to the PRN regimen.

Keywords Age-related macular degeneration · Intravitreal injections · Ranibizumab · Retreatment protocol

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Introduction

Age-related macular degeneration (AMD) is the leading and an increasing cause of blindness in developed countries [1, 2]. Since the results of the MARINA [3] and ANCHOR [4, 5] studies, which demonstrated the efficacy of ranibizumab in maintaining or improving vision at 2 years, the reference treatment for exudative AMD consists of monthly intravitreal ranibizumab injections (IVRs). More recently, the 1- and 2-

year CATT study results [6, 7] showed that bevacizumab and ranibizumab had similar effects on visual acuity, with nearly 30 % of patients gaining vision. Even if this regimen is efficient, providing monthly intravitreal injections has revealed to be difficult in daily practice, because of the burden of repetitive injections on older patients and logistical issues faced by the healthcare teams. Three years after the initial results of the MARINA and ANCHOR studies, Fung et al. proposed an alternative treatment method to limit the number of IVRs [8] in the prospective PrONTO study. This treatment regimen, known as pro re nata (PRN), was quickly adopted by ophthalmologists treating AMD. After an induction cycle of three injections, retreatment was decided if there was a decrease in visual acuity and/or presence of retinal exudation on OCT. Retreatment criteria were checked by monthly follow-up visits. The results of the PRN method were confirmed by the 1- and 2-year results of the CATT study, which also demonstrated equal efficacy of intravitreal injections of either ranibizumab or bevacizumab in preserving visual acuity based on monthly follow-up visits. However, even if this PRN regimen reduces the number of injections, it does not reduce the number of follow-up visits. Furthermore, delivering an IVR rapidly when the retreatment criteria are met has also become problematic. The implementation of the PrONTO recommendations in practice most often remains wishful thinking, and PRN results in routine practice may not be as good as in the PrONTO study [9, 10]. The study reported herein presents the results of a cohort of patients treated for up to 2 years with a systematic series of three monthly IVRs when wet AMD retreatment was needed, and using a reduced follow-up protocol during the injection periods. The recent prospective and randomized IVAN study [11] used the same retreatment protocol, and found a similar efficacy of bevacizumab and ranibuzumab in AMD at 1 year, either with a monthly regimen or with the present protocol. The IVAN retreatment criteria were mainly based on OCT and visual acuity changes, but slightly differed from the PrONTO criteria which were used in the present study.

Patients and methods

In this retrospective study, patients treated for exudative AMD from June 2007 to May 2011 in the Ophthalmology Department of the Strasbourg University Hospital were included. All eyes had documented choroidal neovascularization (CNV) secondary to AMD. All clinical types of new vessels were included, except those associated with large atrophic scars and/or subretinal fibrosis. Eyes with retinal diseases other than AMD, such as diabetic retinopathy, retinal vein occlusion, or pathological myopia, were excluded from the study.

All patients underwent the following treatment and follow-up protocol (Fig. 1):

Initial assessment

The initial assessment included best-corrected visual acuity (BCVA) measurement using the ETDRS scale, a full clinical examination, an optical coherence tomography (OCT) examination (Spectralis-HRA®, Heidelberg, Germany) with measurement of the central retinal thickness (CRT) and a fluorescein angiography (FA) and indocyanine green angiography (ICG) (Spectralis-HRA®, Heidelberg, Germany).

Treatment

All patients received three initial IVRs. When needed, they were reinjected with a new series of three monthly IVRs. Retreatment criteria were based on the PrONTO recommendations:

- Loss of five or more ETDRS letters of BCVA
- OCT signs of onset or persistence of intra-/subretinal exudation and/or CRT increase more than 100 μm
- New macular hemorrhage
- New or expansion of new vessels.

It is interesting to note that these recommendations were similar to those used in the IVAN study except for the visual decrease, which had to be 10 ETDRS letters or more for retreatment. In the IVAN study, vision was used as a retreatment criteria only if exudation and/or hemorrhage were not present. In the absence of OCT or visual deterioration, enlargement of choroidal lesion or fluorescein leakage (>25 % of the lesion circumference) were required to retreat.

Follow-up

One month after the last IVR of each series, all patients systematically underwent a follow-up visit with BCVA measurement and OCT examination. Non-responders to the treatment underwent further explorations, including FA and/or an ICG examination. If the retreatment criteria were met, three other monthly IVRs were scheduled with the next follow-up visit 1 month after the last IVR. When no retreatment was performed, monthly follow-up visits with BCVA measurement and OCT examination were conducted.

Mean initial and final BCVA were compared. Gain or loss of ETDRS letters at the end of the follow-up were calculated. The mean initial and final central retinal thickness (CRT) were compared.

We also determined the mean number of IVRs and complete ophthalmologic follow-up visits (which include ETDRS measurement, OCT examination, funduscopy and/or fluorescein angiography) per year and per patient.

Descriptive statistics and statistical tests were performed using Statview software (Statview, SAS, Inc., 5.0). The

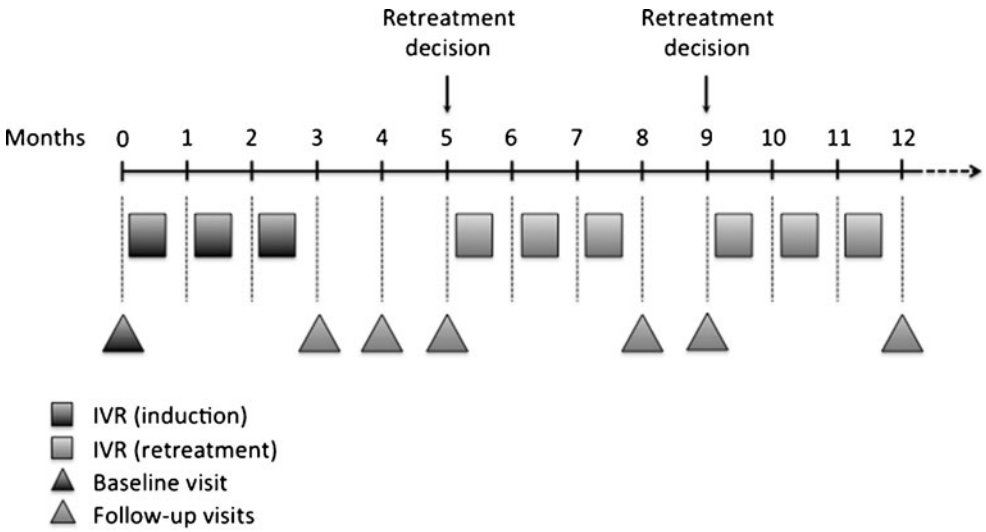

Fig. 1 Schematic representation of the ranibizumab intravitreal injections (IVRs) and follow-up visit protocol used in the present study. After a series of three monthly IVRs following the baseline visit, follow-up visits were scheduled monthly and stopped when retreatment was needed: three new monthly retreatment IVRs were systematically given. Monthly follow-up visits were scheduled 1 month after the last IVR until new retreatment

paired Student's *t*-test was used to compare the initial and final BCVA and CRT. A 5 % alpha risk was set for statistically significance.

Results

Sixty-six eyes of 60 patients including 36 women and 24 men were studied. The mean age of patients was 79 years (SD: 6.7 years; range, 65–93 years])

The mean follow-up was 27 months (SD: 9.67 months; range, 11–48 months). Forty-five eyes (68.18 %) achieved a follow up equal or longer than 24 months.

All types of neovascularization were included in this study: 35 eyes had occult CNV (53.03 %), 19 classic CNV (28.78 %) and five minimally classic (CNV) (7.58 %), five vascularized pigment epithelium detachments (7.58 %), and two retinal angiomatous proliferations (3.03 %).

Visual acuity measurements

At the initial assessment, 18 eyes had an initial BCVA less than or equal to 35 ETDRS letters (20/200 Snellen) and 18 eyes had a visual acuity of more than 70 letters (20/40 Snellen). The mean initial BCVA was 53.18 letters ETDRS (SD: 20.62; range, 0–80), while the mean final BCVA was 54.18 letters (SD: 21.94; range, 0–85). This improvement was not statistically significant ($p=0.69$). At the end of follow-up, 28.8 % of the eyes gained 15 letters (3 lines) or more. BCVA improved or stabilized in 66.6 % of the eyes but decreased in 33.3 % (Fig. 2). Severe visual loss (≥15 letters) was noted in 13.55 % of the eyes (9/66 eyes) (Fig. 2). Of these nine eyes, six had a subretinal fibrosis, one had a submacular hemorrhage, and two had a chronic cystic degeneration.

Finally, 25 of the 66 eyes studied (37.87 %) had a final ETDRS VA of 70 letters or more (20/40 Snellen).

The final visual acuity was correlated with the initial visual acuity ($r=0.59$, Spearman non-parametric correlation test $p<0.0001$) (Fig. 3).

Only a small number of patients had a follow-up longer than 24 months and had six or seven retreatment series in the present study. Nevertheless, our data suggest that BCVA decreases when more IVR series are needed (Fig. 4).

CRT measurements

The mean baseline CRT was 311.67 μm (SD: 8 μm 2; range, 162–586 μm) and the final CRT was 310.2 μm (SD: 111.8 μm; range, 152–849 μm). The difference between the initial and final CRT was not significant ($p>0.05$) (Fig. 4).

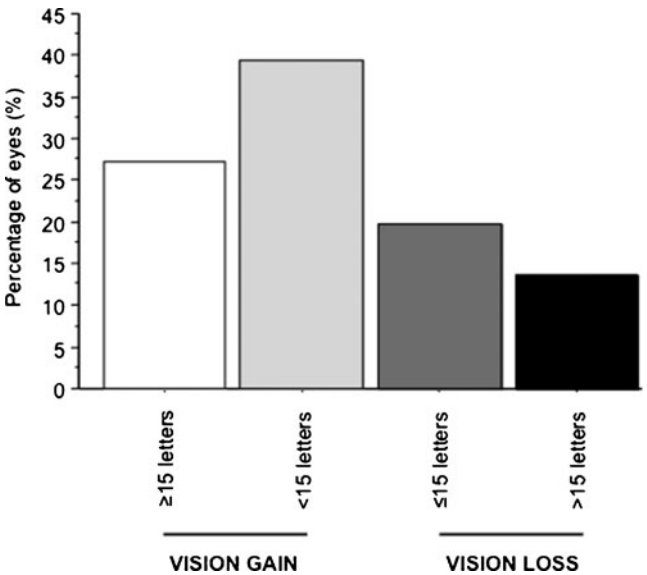

Fig. 2 Visual acuity changes from baseline. After a mean follow-up of 24 months, 28.8 % of the eyes gained 15 letters or more. VA improved or stabilized in two-thirds of the eyes, while it decreased in one-third

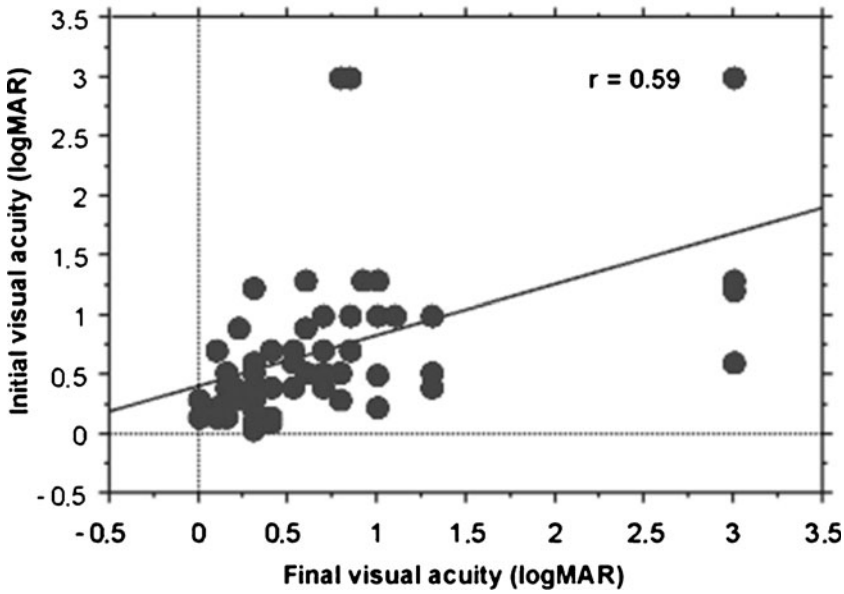

Fig. 3 Relation between initial and final visual acuity. Final BCVA correlated moderately with initial BCVA ($p<0.05$, Spearman correlation test, $r=0.59$)

Number of injections and number of follow-up visits

The mean number of injections per year was 4.93 (SD: 1.88; range, 1–9). Patients received 5.5 IVRs (SD: 1.67; range, 3–9) during the first year and 3.65 during the second year (SD: 2.46; range, 0–9).

The mean number of follow-up visits with complete ophthalmological examination per year was four (SD 0.80; range, 1.66–6). The mean interval between two series of IVRs shortened when more series were needed (this decrease was significant for the third series, Wilcoxon test $p=0.03$), suggesting that newly treated neovascular lesions may respond better to anti-VEGF therapy than new vessels treated by numerous IVRs (Fig. 5).

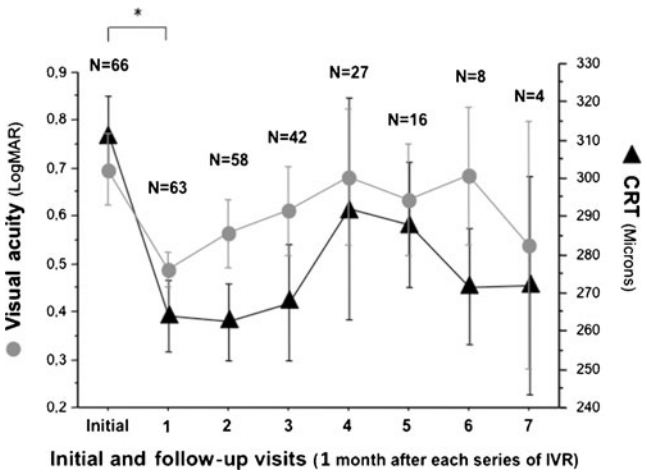

Fig. 4 Best-corrected VA and central retinal thickness (CRT) plotted against successive retreatment injection series. Visual and CRT improved significantly after the first series of ranibizumab injections ($p<0.05$, t-test). Visual acuity and CRT were no longer significantly different from baseline after further retreatment series

No serious ocular side-effects due to intravitreal injections were noted in this study.

Discussion

The MARINA [3] and ANCHOR [4, 5] studies have proven the efficacy of ranibizumab, and found a significant improvement in visual acuity at 24 months with monthly IVRs. Several studies have looked for a different injection protocol to reduce the number of injections, but to our knowledge, none has sought to reduce the number of follow-up visits.

The PIER study [12], based on a pattern of quarterly injections after an induction series of three monthly IVRs, only stabilized visual acuity (−0.2 letters) at 1 year. These disappointing results compared to monthly IVRs have been confirmed by the EXITE study[13].

The monocentric and prospective PrONTO study [8, 14] found that significant improvement in visual acuity (11.1 letters) could be achieved with a PRN retreatment protocol with a reduced number of IVRs within the first year (mean, 5.6) and the second year (mean, 9.9). More recently, the retrospective study by Querques et al. [15] and then the prospective, randomized CATT studies [6, 7] confirmed the efficacy of the PRN regimen with monthly follow-up visits. However, PRN in everyday practice might be less beneficial, as reported in the PrONTO study. Indeed, a few studies which assessed the results of PRN treatment in daily practice found no statistical improvement of BCVA after 1 year [9, 10]. Moreover, the proportion of patients gaining three or more lines of BCVA was much lower in the study by Cohen et al. than in PrONTO (8 % vs 35 %) [8, 9]. Cohen et al. [9] noted that the patients in their study were examined and treated less frequently than in the PrONTO study.

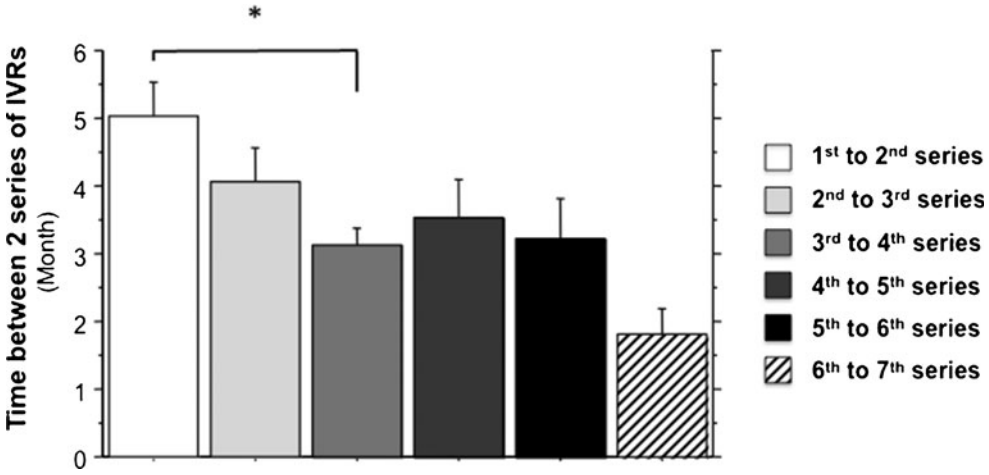

Fig. 5 Time between two series of ranibizumab retreatment injections (IVRs). The time period shortens as the number of retreatments increases. The time significantly decreased only for the third series of IVRs (Wilcoxon test, $p=0.03$). The number of patients who underwent more than three IVR series was too low to reach statistical significance

These differences between the prospective study results and the routine practice results may stem from several factors, including the difficulty of following up patients every month, especially older patients who often find it difficult to travel long distances for the repeated follow-up visits and/or injections, and the logistical problems implied by the necessity of rapidly performing an increasing number of IVRs. Moreover, in a clinical setting, the IVRs are usually performed in a dedicated session with many patients scheduled, usually not on the same day as the control visit. Consequently, two visits are often necessary to perform the control examination and the IVR retreatment. This is time-consuming for both patients and physicians, and was not the case in prospective randomized studies.

Frequently, these factors lead to unreasonable delays [16–18] between the follow-up visits, and may explain the disappointing results reported by Cohen et al. and Bloch et al. [9, 10].

In the present study, we assessed a retreatment protocol in accordance with PrONTO retreatment criteria, consisting of a systematic series of three monthly IVRs (Fig. 1). This protocol was also proposed by Heimes et al. in 2011 [19], who did not find significant visual gain at 1 year. Conversely, the IVAN randomized trial [11] referred to this protocol, and demonstrated that it was as effective as a monthly regimen at 1 year, with a mean IVR rate of 7. Even if these studies are barely comparable as their design were different, we may hypothesize that the discrepancy between these two results is related to the restrictive retreatment criteria applied in the German study. As in the study by Heimes et al. [19], no significant increase of BCVA (+0.98 letters) was observed in the present study, after a longer follow-up period of up to 27 months. It seems that this treatment scheme is less effective in daily practice than the PrONTO protocol. However, the inclusion criteria were different from those of the PrONTO study. For example, we did not set a minimum value for VA at the inclusion, whereas a VA had to be greater than 20 ETDRS letters in the PrONTO study. Moreover, the longer follow-up in the present study could influence the results negatively, as suggested by a study reported by Dunavoelgyi et al. [20], which observed an initial

Table 1 Comparison of the results of the present retrospective study with those of the MARINA and ANCHOR clinical trials, the PrONTO open-label prospective study, and the retrospective study by Cohen et al. No significant visual change was noted after a mean follow-up of 27 months, but the proportion of eyes gaining three lines or more was closer to those of pivotal studies compared with the "routine practice" results of PRN shown by Cohen et al.

	MARINA Prospective trial	ANCHOR Prospective trial	PrONTO Prospective study	Cohen et al. Retrospective study	Present study Retrospective study[a]
Eyes that improved by 15 or more letters (%)	33.8	40.3	35	8	28.79
Eyes that lost fewer than 15 letters (%)	94.6	96.4	95	90.3	86.77
Eyes with final VA≥ 20/40 (%)	40	40.3	?	25.8	37.86
Mean VA changes (ETDRS chart letters)	+7.2	+11.3	+9.3	+0.7	+0.98
Number of injections	12	12	5.6 (mean)	3.79 (mean)	4.93 (mean)
Number of follow-up visits	12	12	12	8.06 (mean)	3.43 (mean)

[a] The mean follow-up of the 66 eyes included in the study was 27 months [min 11, max 48]. Forty-five eyes (68.18 %) had a follow-up superior or equal to 24 months

improvement in VA followed by a secondary decrease in the number of patients treated with the PRN protocol for 3 years.

Interestingly, a higher rate of eyes gaining 15 letters or more was noted in our study than in the study by Cohen et al. (28.79 % vs 8 %) [9] (Fig. 2). Our result was more in accordance with those of the MARINA (33.8 %) and PrONTO (35 %) studies, but inferior to those of the ANCHOR study (40.3 %) [3, 5, 14] (Table 1). The rate of patients with final visual acuity greater than or equal to 20/40 (37.86 %) was comparable to the MARINA and ANCHOR results (40 % and 40.3 % respectively) [3, 5].

The mean number of IVRs per year was 4.9, which is less than in the PrONTO study (5.6 IVRs/year) [14], and even less than in the IVAN study (seven IVRs/year) [11]. As patients were not reviewed by their physician during the 3-month periods of reinjections, the number of complete ophthalmologic follow-up visits (excluding the visits for IVRs) was also lower (four visits a year) than with a PRN or "inject and extend" protocol (eight to nine visits a year) [8, 14, 21]. If we assume that, in many clinical centers, the IVR retreatment is not performed on the same day as the control visit (in which the retreatment has been decided), the overall number of visits is then reduced using our protocol.

The rate of patients with visual loss (≥15 letters) at the end of the follow-up was higher than in the MARINA and ANCHOR studies (13.55 % vs 9 and 10 % respectively) [5, 22] (Fig. 2). Results from our study and from larger randomized studies are difficult to compare; however, the discrepancy observed may be due to the absence of VA inclusion criteria: 27.27 % of the eyes included in the present study had an initial VA of 20/40 or more. These eyes are at greater risk of losing three lines or more even if they display a satisfactory final VA. This higher rate of severe visual loss could also be related to a lack of assiduity to the monthly control visits by some of our patients. The final BCVA correlated moderately but significantly with initial BCVA (Fig. 3), suggesting that initial BCVA is a predictive factor of good final VA, as already stated by Bloch et al. [10].

Not surprisingly, eyes needing more series of retreatment were less likely to experience VA improvement and or reduction of the retinal exudation on OCT (Fig. 4). Throughout the study, the time between two series of reinjections decreased as the number of required retreatments increased, which might suggest a tachyphylaxis phenomenon for CNV needing more retreatments (Fig. 5).

In summary, the present study showed that series of three monthly IVRs for AMD retreatment without concomitant follow-up visits stabilized BCVA after 2 years of follow-up. These results are disappointing, given that the IVAN study showed that this protocol was as effective as monthly dosing. It demonstrates that the results of real-life practice may differ from prospective study results, as shown for the PRN protocol. Nevertheless, nearly 30 % of the eyes achieved a 3-line visual gain; the number of follow-up visits was significantly reduced without an increase in the number of required annual injections.

A prospective study comparing this treatment scheme to a PRN regimen is mandatory to confirm these results and alleviate unnecessary follow-up visits in everyday practice.

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References

1. Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP (2004) Global data on visual impairment in the year 2002. Bull World Health Organ 82:844–851
2. Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR (2012) The estimated prevalence and incidence of late-stage age-related macular degeneration in the UK. Br J Ophthalmol 96:752–756
3. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY (2006) Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 355:1419–1431
4. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S (2006) Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 355:1432–1444
5. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T (2009) Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology 116:57–65
6. Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ (2011) Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 364:1897–1908
7. Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, Toth C, Redford M, Ferris FL 3rd (2012) Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 119:1388–1398
8. Fung AE, Lalwani GA, Rosenfeld PJ, Dubovy SR, Michels S, Feuer WJ, Puliafito CA, Davis JL, Flynn HW Jr, Esquiabro M (2007) An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol 143:566–583
9. Cohen SY, Dubois L, Tadayoni R, Fajnkuchen F, Nghiem-Buffet S, Delahaye-Mazza C, Guiberteau B, Quentel G (2009) Results of one-year's treatment with ranibizumab for exudative age-related macular degeneration in a clinical setting. Am J Ophthalmol 148:409–413
10. Bloch SB, la Cour M, Sander B, Hansen LK, Fuchs J, Lund-Andersen H, Larsen M (2011) Predictors of 1-year visual outcome in neovascular age-related macular degeneration following intravitreal ranibizumab treatment. Acta Ophthalmol. doi:10.1111/j.1755-3768.2011.02268.x
11. Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, Reeves BC (2012) Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN Randomized Trial. Ophthalmology 119:1399–1411

12. Regillo CD, Brown DM, Abraham P, Yue H, Ianchulev T, Schneider S, Shams N (2008) Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol 145:239–248
13. Schmidt-Erfurth U, Eldem B, Guymer R, Korobelnik JF, Schlingemann RO, Axer-Siegel R, Wiedemann P, Simader C, Gekkieva M, Weichselberger A (2011) Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. Ophthalmology 118:831–839
14. Lalwani GA, Rosenfeld PJ, Fung AE, Dubovy SR, Michels S, Feuer W, Davis JL, Flynn HW Jr, Esquiabro M (2009) A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. Am J Ophthalmol 148:43–58
15. Querques G, Azrya S, Martinelli D, Berboucha E, Feldman A, Pece A, Coscas G, Soubrane G, Souied EH (2010) Ranibizumab for exudative age-related macular degeneration: 24-month outcomes from a single-centre institutional setting. Br J Ophthalmol 94:292–296
16. Arias L, Armada F, Donate J, Garcia-Arumi J, Giralt J, Pazos B, Pinero A, Martinez F, Mondejar JJ, Ortega I, Zlateva G, Buggage R (2009) Delay in treating age-related macular degeneration in Spain is associated with progressive vision loss. Eye (Lond) 23:326–333
17. Muether PS, Hermann MM, Koch K, Fauser S (2011) Delay between medical indication to anti-VEGF treatment in age-related macular degeneration can result in a loss of visual acuity. Graefes Arch Clin Exp Ophthalmol 249:633–637
18. Dadgostar H, Ventura AA, Chung JY, Sharma S, Kaiser PK (2009) Evaluation of injection frequency and visual acuity outcomes for ranibizumab monotherapy in exudative age-related macular degeneration. Ophthalmology 116:1740–1747
19. Heimes B, Lommatzsch A, Zeimer M, Gutfleisch M, Spital G, Dietzel M, Pauleikhoff D (2011) Long-term visual course after anti-VEGF therapy for exudative AMD in clinical practice evaluation of the German reinjection scheme. Graefes Arch Clin Exp Ophthalmol 249:639–644
20. Dunavoelgyi R, Sacu S, Eibenberger K, Palkovits S, Leydolt C, Pruente C, Schmidt-Erfurth U (2012) Retreatment with anti-vascular endothelial growth factor therapy based on changes in visual acuity after initial stabilization of neovascular age-related macular degeneration: 3-year follow-up results. Retina 12:2223–2227
21. Oubraham H, Cohen SY, Samimi S, Marotte D, Bouzaher I, Bonicel P, Fajnkuchen F, Tadayoni R (2011) Inject and extend dosing versus dosing as needed: a comparative retrospective study of ranibizumab in exudative age-related macular degeneration. Retina 31:26–30
22. Rosenfeld PJ, Shapiro H, Tuomi L, Webster M, Elledge J, Blodi B (2011) Characteristics of patients losing vision after 2 years of monthly dosing in the phase III ranibizumab clinical trials. Ophthalmology 118:523–530